

The Skin

The most accessible tissue of the body serves as a potential focus for multidisciplinary research.

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The concepts and techniques of mathematics, physics, and engineering are being applied as never before to biology and medicine. This is evidenced by rapidly developing hybrid disciplines such as biomathematics, biophysics, bioengineering, biomechanics, and bioclimatology. The opportunities for such interdisciplinary collaboration are far more extensive than is generally recognized. We have selected the skin as an example to show the diversity of biological problems which can be approached collaboratively by investigators with widely different backgrounds.

The skin is an appropriate choice for many reasons. Everyone is familiar with many of its characteristics. Samples are immediately at hand for direct examination or quantitative measurements. It has both living and nonliving components susceptible to physical and chemical measurements. It contains many different tissues, including blood vessels, glands, sense organs and nerves, smooth muscle, connective tissue, and fat. Although many of its properties have been examined in the past, much remains to be learned. For example, diseases and lesions of the skin are generally identified primarily on the basis of their appearance. Comprehensive descriptions of the biological, physical, and chemical properties of the skin are badly needed to clarify its function in health and to serve as criteria for determining the presence of disease.

Human skin is a highly specialized organ with remarkable properties and diverse functions. Many primitive organisms live in a watery environment which ordinarily protects them against rapid fluctuations in temperature, humidity, concentration gradients, acceleration, toxic chemicals, radiation, and so forth. If their immediate environment suddenly changes, they die for lack of compensatory mechanisms. When living forms emerged from primordial swamps, their external skin became specialized as a barrier between delicate living cells and a capricious, often unfriendly environment. In the most highly developed organisms, the body cells flourish within a thermostatically controlled culture medium resembling in many respects an ancient tropical sea. With the skin as an effective barrier, the immediate environment of cells remains remarkably undisturbed during wide fluctuations in environmental conditions. Human tolerance to environmental changes evokes interest among many types of investigators, including anatomists, physiologists, dermatologists, and surgeons, and extends into areas of physics, chemistry, various fields of engineering, and far beyond.

This article is intended to direct the attention of quantitative scientists to the opportunities for effective collaboration on problems related to biological structures and organisms.

Structure of the Skin

Human skin is best understood in terms of its basic division into three distinct tissue layers: the epidermis, the dermis, and the subcutaneous fat. Epidermis, the outermost skin layer, evolves from a dense population of actively dividing epidermal cells. Remnants of these epidermal cells accumulate at the skin surface as a thin, stratified, and highly specialized layer called the stratum corneum (Fig. 1A).

The epidermis is supported by a second layer of skin, called the dermis, which is thicker and composed chiefly of collagen fibers and intertwined elastic fibers enmeshed in a gel-like matrix (Fig. 1A). When this skin layer is chemically processed, its fibrous components convert to leather.

The deepest skin layer, the subcutaneous fatty tissue, is characterized by closely packed cells which contain considerable fat. The boundary between this layer and the dermis is not well demarcated, and the layer varies widely in thickness. The subcutaneous fat layer provides thermal insulation for conservation of body heat when the flow of blood to the skin is curtailed (Fig. 1A).

The salient anatomic features of the skin relevant to the objectives of this article are summarized below. For more comprehensive coverage, the reader is referred to Montagna (1) and Odland (2).

A prime function of the external skin layer is to maintain a protective barrier of considerable toughness and resilience over the entire surface of the body. This is provided by the stratum corneum, the cells of which are being continuously worn, scraped, or rubbed off. The stratum corneum must then be replaced by multiplication of the underlying epidermal cells. Thus the

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principal anatomic features of the epidermis relate to the elaboration of the stratum corneum.

Epidermal regeneration depends on cellular division in the basal cell layer (Fig. 1*B*). The dividing cells migrate or are displaced toward the skin surface. During their transit, these cells differentiate into layers of flat, laminated plates. The epidermal cells elaborate an internal fiber system called tonofibrils, which appears to serve a structural or supportive function. Other important structural components of the epidermis are numerous localized thickenings of the cell membrane (desmosomes). These "spot welds" between epidermal cells serve as anchoring points for the tonofibrils and contribute to the cohesion of contiguous epidermal cells. The process of cellular differentiation produces cell remnants with cell membranes twice as thick as those of other epidermal cells. The space within the cell membranes is filled with a sub-

stance called keratin, which is composed of a complex matrix of tonofibrils and material from keratohyalin granules (Figs. 1*B* and 2*A*). Keratin is tough and extremely resistant to changes in pH, heat, and cold and to enzymatic digestion.

The dermis supports and binds the epidermis so that it conforms to the underlying bones and muscles. The collagen and elastic fibers of the dermis make the skin both tough and elastic. Collagen is composed of bundles of banded fibers, shown at high magnification in Fig. 2*C*. These fibers consist of long-chain molecules twisted into a complex helical form to provide tensile strength equal to that of thin steel wire (3). Collagen, the principal constituent of tendons, is one of the most abundant proteins in the animal kingdom, first appearing in primitive coelenterates (for example, jellyfishes and sponges).

Blood vessels are distributed diffusely

throughout the dermis and, to some extent, throughout the subcutaneous fat tissue, providing the skin with a blood supply far in excess of its metabolic needs. However, the abundant blood supply also provides a convenient channel for convective transfer of internal body heat to the surface of the skin. Thus the cutaneous blood vessels are an important element of the body's thermoregulatory system (Fig. 1*A*).

The fatty layer underlying the dermis serves as a thermal barrier to protect underlying tissues from excessive environmental heat, and it retards loss of body heat in cold environments. Bundles of collagen threading between the accumulations of fat cells provide a flexible linkage between the superficial skin layers and the underlying structures. Thus the fat layer serves as a cushion for the dermis and epidermis and permits considerable lateral displacement in many regions of the body surface.

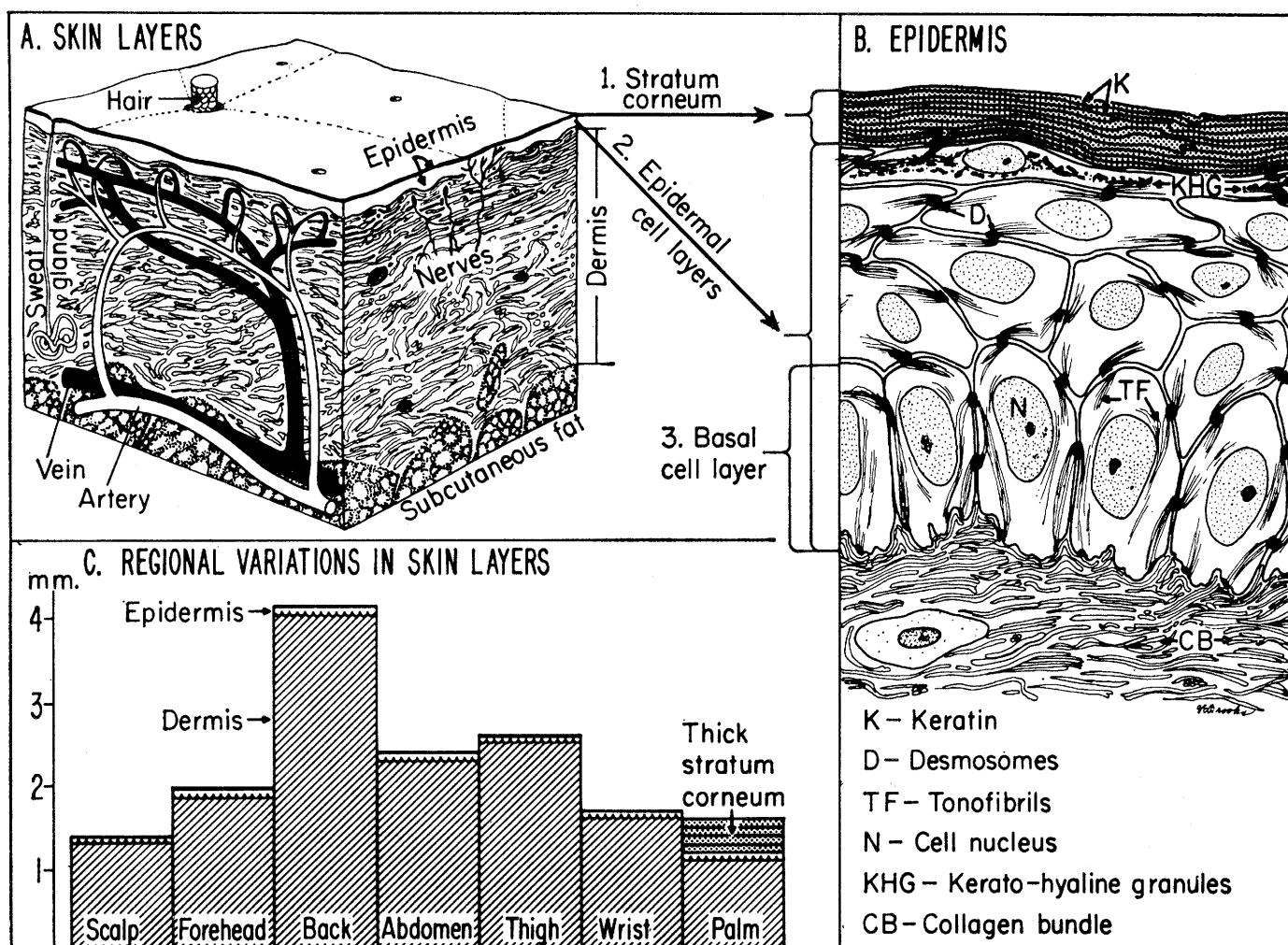


Fig. 1. *A*, The components of the skin are illustrated schematically to indicate their anatomical relations. *B*, Cells in the germinal layer of the epidermis divide, and the daughter cells migrate toward the surface, specializing into flat cells of the stratum corneum. *C*, The skin layers vary greatly in thickness in various regions of the body.

Variations in Cutaneous Anatomy

It is important to recognize the regional differences in cutaneous anatomy. Differences in distribution of hair, sebaceous glands, and apocrine (odoriferous) and eccrine (true) sweat glands are readily apparent. Equally important, though much less obvious, are the striking differences in thickness of constituent skin layers in different regions of the body. The remarkable differences in dermal thickness are depicted schematically in Fig. 1C. Epidermal thickness, 60 to 100 microns, is remarkably constant over the body, except on the palms and soles, where the stratum corneum alone may reach 600 microns in thickness. Further local variations are shown in Table 1.

Human skin is remarkably effective in retarding diffusion of gases, water, and many other types of chemicals. If the skin were as permeable as the membranes in the lungs, exposure to dry air would rapidly lead to fatal

dehydration. Body constituents are effectively retained within the skin. Most irritants and cellular poisons (with notable exceptions such as mustard gas and "poison ivy") are unable to penetrate intact skin.

The most prominent features that distinguish man from lower animals are the brain and the epidermis, both of which originate embryologically from the ectoderm. Many experimental observations on the skin defy explanation at the present time. For example, heavy sweating from heat or exercise is drastically reduced (by 80 percent) if the skin is covered with water, either by immersion or by accumulation of sweat (4). Conversely, a localized skin area flushed with dry air sweats more profusely (5). These observations suggest that sweating may be affected by local conditions on the skin surface. Is it possible that water entering and passing through the stratum corneum produces swelling which could obstruct the ducts of the sweat glands? The mechanisms

by which water enters the skin from moist air or from concentrated salt solutions deserve consideration.

If the skin is exposed to air with more than 90 percent relative humidity or to a salt solution of less than 10 percent concentration, water moves into the skin at the rate of 10 to 50 grams per square meter per hour (6). The flow rate of water appears to be controlled by the water density gradient in the skin and by its resistance to liquid diffusion, as though it were moving through submicroscopic holes. However, water uptake is highest on the soles of the feet, where the epidermis is thickest (Fig. 1C). Water moves out of the skin into air of less than 90 percent relative humidity or into a salt solution of greater than 10 percent concentration. This outflow into dry air is known as insensible skin perspiration. The point at which water neither enters nor leaves the skin is called the neutral point; this neutral point is lowered in patients suffering from edema (for example, in toxemia,

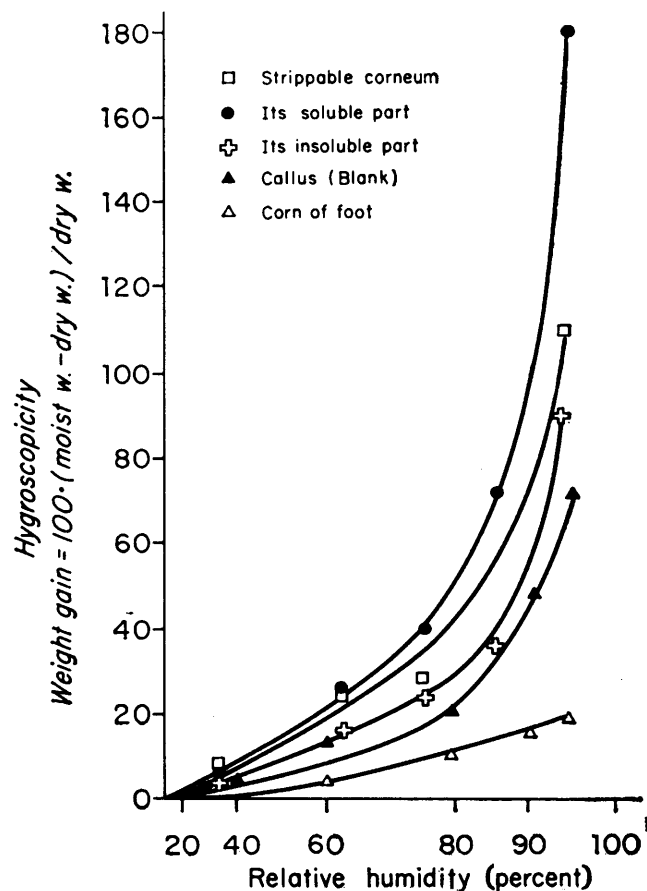
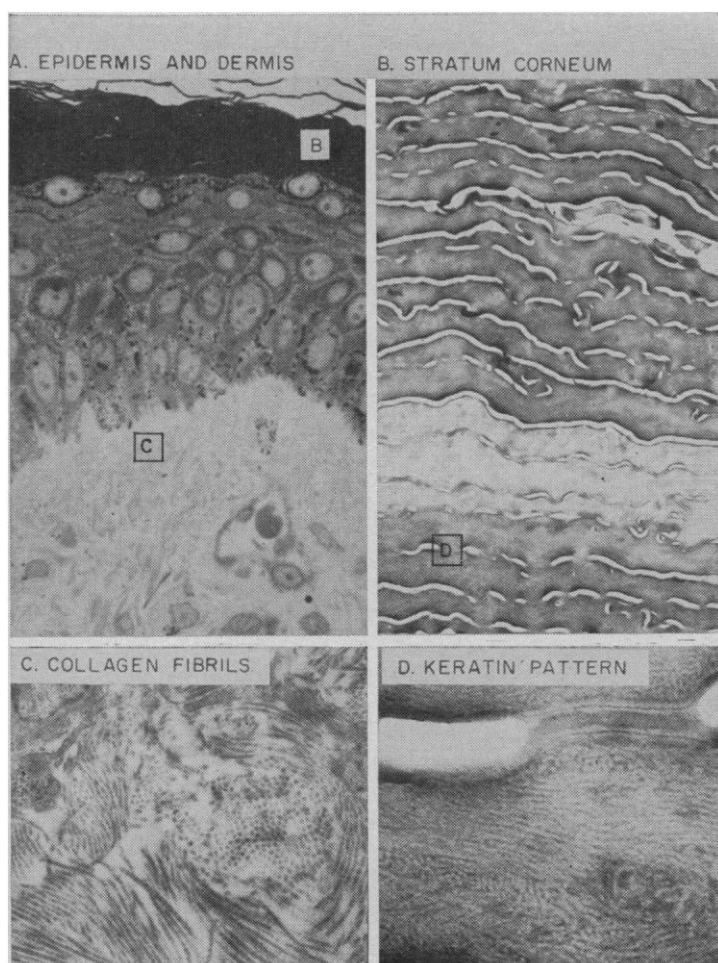


Fig. 2 (left). *A*, The epidermis and dermis ($\times 11,000$). *B*, The stratum corneum is composed of layers of platelike cells. *C*, The dermis is composed of collagen fibers arranged in intertwining bundles ($\times 20,000$). *D*, The keratin pattern within the cells of the stratum corneum ($\times 180,000$). Fig. 3 (right). Weight gain of different types of skin during changes in relative humidity with temperature maintained at 20°C.

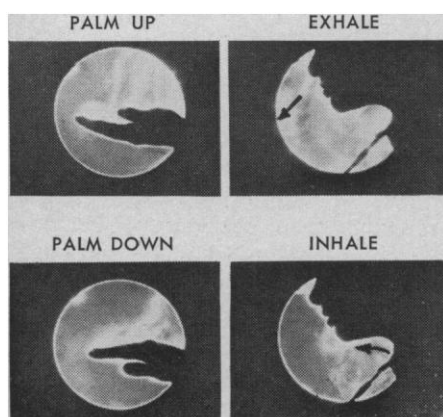


Fig. 4. Schlieren photographs bring out thermal gradients which produce convection currents that aid in the elimination of heat from the body. (Equipment and photographs prepared by Don Harding.)

pregnancy, menstruation, and infectious illness).

The stratum corneum is generally accepted as the principal barrier to diffusion of substances. Blank (7) has recently shown that sorption as occurs in gels, rather than diffusion resistance, is the decisive factor determining the transfer of a particular substance. Perhaps all transfer through the skin occurs in the liquid phase rather than a vapor phase and is caused by a concentration gradient in the stratum corneum. In this case, the chemical (for example, alcohol or water) is the solute and the surface layer of skin (stratum corneum) is the solvent. For example, the solubility of ethanol in the stratum corneum was too small to measure on a delicate balance, and its transfer through living skin is negligible. Water, on the other hand, is easily sorbed and transmitted. The stratum corneum, which can be stripped off with cellulose adhesive tape, is far more hygroscopic than other keratinized ma-

terials such as hair, horn, or callus (8). Furthermore, the curve of water intake plotted against relative humidity rises sharply at humidities above 90 percent (Fig. 3).

These observations suggest the following hypothesis as a basis for discussion and further investigation. Water or water vapor on the skin raises the water concentration in the superficial corneal layer. The deeper layers of the stratum corneum are assumed to be less hygroscopic than the surface layer, perhaps because of gradients in pH or tonicity. Such variances are known for the gels of other tissues. Equilibrium may be reached with greater concentration of water in the superficial layers than in the deeper layers. Indeed, the solute is not truly miscible with the solvent; only a minute amount is water-soluble, contrary to Szakall (9). The skin appears to be totally impermeable to salts, so that pure water enters the stratum corneum from salt solution. If we assume that the first viable layer can take up water from the lowest cornified layer, the transport of water from concentrated solutions might be explained on the basis of osmotic forces in the germinal cell layers.

The variability in skin morphology (Fig. 1C) also is expressed in differences in the skin's function as a diffusion barrier. Distinguishing features of arm, sole, scrotum, and callus are summarized in Table 1. The scrotum appears to be a primitive form of skin which readily transfers water and chemicals. Indeed, the evaporative cooling of the scrotum appears to be attributable to diffusion and not to sweating. Note that the hygroscopicity of callus is lower than that of stratum corneum of the arm (10), but the water-vapor transfer is much higher (Fig. 3). Therefore its resistance to liquid diffusion is low. The

data available for such comparisons are meager. These considerations indicate some of the many problems which remain to be solved about the diffusion properties and function of the skin.

Electrical and Thermal Barrier

Dry skin has a high electrical impedance to the flow of electric current. This property provides some protection. It is also a source of annoyance to basic scientists and clinicians attempting to measure biological potentials from the body surface (as in electrocardiograms or electroencephalograms). Despite extensive work on minimizing this electrical barrier, little effort has been directed at establishing its structural location or mechanism. Since electrodes drastically change the impedance of the stratum corneum, the true impedance of dry skin in vivo or in vitro has not been measured accurately. By stripping off layers of the stratum corneum with cellulose tape, Lawler, Davis, and Griffith (11) reduced the mean impedance by a factor of 6. This observation indicates that the electrical impedance tends to be greatest in the superficial layers which are also the main barriers to ion diffusion. More detailed information on this subject is badly needed (12).

In primitive animals, body temperature fluctuates with environmental temperature, metabolism varying correspondingly because of varying rates of enzymatic reactions. However, warm-blooded mammals maintain a fairly constant internal temperature whether living in the tropics or the arctic. Most enzymes are so sensitive to temperature change that a drop of only a few degrees may inhibit their activity completely. The role of the skin in conserving and eliminating heat must be considered in terms of its heat conductivity, convection in the blood vessels, and excretion of sweat. These inner factors, then, influence the outer heat loss by infrared radiation, convection, and sweat evaporation.

A fundamental requirement in warm-blooded animals is that they establish and maintain a balance between factors which add heat to the body (that is chemical reactions in the body) and heat elimination through the skin and exhaled air. Much heat is stored in the body because of its thermal capacity. Effective temperature-control mechanisms minimize change in heat storage

Table 1. Comparison of water transfer and characteristics in human skin from four different areas. This demonstrates that comparative dermatology includes not only comparison of the skins of different animal species but also that of different regions of skin in one person.

Characteristic	Area			
	Arm	Sole	Scrotum	Callus
Transepidermal water transfer				
in vivo (inflow)	Low	High	High	?
(outflow)	Low	High	High	?
in vitro	Low	?	?	High
Alcohol transfer in vivo	Low	Low	High	?
Corneum thickness (μ)	15	100	15	100
Pliable	Yes	Yes	Yes	No
Stretchable	Yes	No	Yes	No
Hygroscopicity of corneum	High	?	?	Low
Sweating stimulus	Thermal	Mental	None	None?
Typical sweat glands	Eccrine	Eccrine	Apocrine	

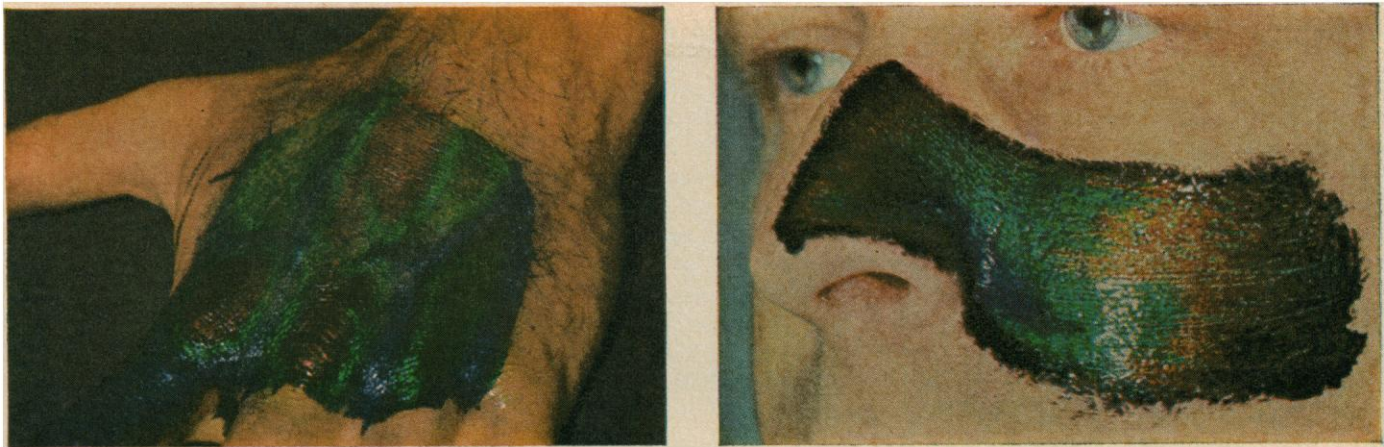


Fig. 5. Skin temperature varies over the body, as shown by liquid crystals which display a full spectrum of color over a range of 3°C (15).

within the body. Such mechanisms in man are highly specialized and cannot be completely understood from studies on laboratory animals with fur coats and with sweating restricted to foot pads (such as the dog).

The skin is equipped with networks of blood vessels in the dermis, with capillary loops extending nearly to the surface (Fig. 1A). With these blood vessels wide open, the skin is a most effective heat exchanger. By controlling blood content and blood flow in the skin vessels, the quantity of heat dissipated can be precisely regulated. When environmental temperatures feel comfortable, heat loss is controlled by adjustments in blood flow through the skin. At warmer temperatures, sweating accelerates heat loss by evaporation; at colder temperatures, more heat is produced by metabolism, muscular activity, or shivering. Heat-dissipation reactions can be elicited by warming selected sites at the base of the brain in animals. Cooling at nearby sites produces shivering at normal environmental temperature. The normal temperature-control mechanisms must integrate the diverse input of information from the various regions. Investigation of biological temperature control should be of interest in terms of thermodynamics, control system analysis, and environmental engineering (13).

The importance of air movement in transferring heat from the body surface is recognized in the sense of relief given by cooling breezes on a hot day. However, skin sensations do not accurately portray conditions in the layers of air in contact with the body surface. By means of a simple Schlieren technique, the temperature gradients and

convection currents can be directly visualized as they affect the refractive index of the air (Fig. 4). Convection currents which develop spontaneously over the exposed palm or back of the hand held motionless in still air disturb the air blanket next to the skin. Routes of elimination of heat during respiratory activity are illustrated by Schlieren photographs taken during expiration and inspiration (Fig. 4). Clearly, simple engineering techniques can be used to obtain information about the functional conditions of an organ system—particularly one as accessible as the skin.

Variability in temperature is not confined to the air blanket near the body surface. Distribution of temperature gradients on the skin can be visualized directly by utilizing the changes in color of selected mixtures of certain "liquid crystals" described by Ferguson (14). We used mixtures of cholesterol esters (15) that exhibited a full spectrum of color as their temperature was changed from 28° to 31°C. The esters are colorless above or below this specified range. The colorful display of cholesterol crystals on the back of the hand discloses warm streaks over the superficial veins and cool regions over the knuckles (Fig. 5A). Temperature varies from point to point and from moment to moment on such a surface. Similar temperature gradients are displayed over the nose and cheek (Fig. 5B). Obviously, such gradients are highly complex because of the variation in properties of the skin and in the environmental thermal load along with the continual physiologic adjustment in sweating rate, skin blood flow, and metabolic rate.

The physiologist and the engineer might profitably join in the attack on

problems related to cutaneous thermal gradients. Such combined scientific interest would, it is hoped, provide quantitative information about the participation of skin blood flow in thermoregulation, and, in addition, would establish more precise techniques for measuring the important parameters of the cutaneous thermal gradients.

A reasonable approach to the study of cutaneous thermal gradients is found in the application of the standard heat-flow equation to heat transport in the skin (13). Using this equation in a digital computer program, Douglas Hansmann, an undergraduate engineering student, derived a mathematical model for investigating the effects of environmental heat on the cutaneous thermal gradients. The derivation of the partial differential equation for transient heat flow was based on the following assumptions: (i) The skin is a homogeneous semi-infinite slab with infinite boundaries; (ii) its material properties vary with depth, either linearly or as step functions,

$$\frac{\partial T}{\partial t} = K_1 \frac{\partial^2 T}{\partial x^2} + K_2 \frac{\partial T}{\partial x}$$

where T is temperature in degrees Celsius, t is time in seconds, x is depth in centimeters, K_1 is thermal diffusivity [or thermal conductivity/(density $\times$ heat capacity)], and K_2 is $\partial K_1 / \partial x$. By using the finite difference approximation technique, a digital program is obtainable from this expression. With such a program the cutaneous thermal gradients can be simulated as they are affected by variations in thermal diffusivity of the different skin layers or by environmental heat loads on these gradients.

The Barrier to Radiation

The skin protects delicate underlying cells by absorbing, to varying extents, electromagnetic radiation such as soft x-rays, ultraviolet light, visible light, and infrared wavelengths (13). The damaging effects of ultraviolet light (wavelengths around 0.30 micron) are familiar to all who have been severely sunburned. Frequent application of ultraviolet may cause loss of elasticity of skin, early aging, and possibly even cancer. Both proteins and skin pigments have maximum absorption of wavelengths in the region of 0.28 micron, so that ultraviolet light is almost completely absorbed within about 100 microns below the skin surface. Excessive exposure to sunlight leads to the elaboration of melanin, the skin pigment responsible for suntan. Visible light is transmitted deeper than ultraviolet or far-infrared wavelengths. Transmission by superficial layers increases sharply for wavelengths longer than 0.32 micron to a maximum in the near infrared (around 1.0 micron), then falls to virtual extinction at about 1.4 microns as a result of the strong absorption by water (16). Our knowledge of the optical properties of skin is incomplete since these properties vary with skin thickness and with the degree of pigmentation. The differential absorption of light by blood and tissues provides a basis for photoelectric plethysmography (17) to supplement other means of estimating skin blood flow (18).

Vital information about the immediate environment is conveyed to the central nervous system from exquisitely sensitive nerve endings responding to touch, warming, cooling, and pain. The sensitivity of some of these transducers is remarkable. For example, large bulbous endings (Paccinian corpuscles) just below the skin are excited by mechanical deformations of 0.5 micron applied for 100 milliseconds. The mechanisms by which slight deformation elicits conducted electrochemical impulse have been explored by Loewenstein (19). Temperature sensations are elicited by two types of receptors; one responds to an increase in skin temperature by as little as 0.00015 calorie per square centimeter per second. Another type of ending responds to a

temperature decrease of 0.004°C per second. Heat-sensitive receptors in certain snakes are even more sensitive. Transducer principles and communication theory should be applied more fully to these energy-converting nerve endings. Engineers could well aspire to develop transducers of such size and sensitivity.

The skin serves as a flexible container for the body. When torque is being applied to the handle of a screwdriver to loosen a balky bolt, consider the forces which must develop and the strength of the attachments between layers of cells in the skin and in the collagen fibers fastening the epidermis to underlying structures.

The mechanical properties of skin are of vital importance to surgeons, particularly in selecting sites for incisions or closing large defects. Kenedi and his colleagues (20) have begun reporting results of quantitative analysis of skin properties, with particular concern for the problems of plastic surgery.

Some Problems

The foregoing discussion highlights a wide variety of problems which could involve many different disciplines. Detailed structural analysis of the skin should include analysis of the molecular composition, the physical chemistry, diffusivity for water and chemicals of all kinds, thermal conductivity, electrical impedance, radiation absorption, and fragility of the stratum corneum. The explanation of the water intake by the skin and of the stoppage of sweating by water on the skin could lead to new insights into a quasi-active transfer. The dermis is of interest with reference to tensile strength, heat exchange, energy conversion in sensory nerve endings, coding of information on nerve trunks, active transport in glands, elastic and viscous moduli, stress-strain relations, and control of blood flow and blood content in superficial vessels. Temperature regulation is a fine example of a complex biological compensatory mechanism subject to control-system analysis. These categories of information would benefit from the data-acquisition and analytical techniques of engineers, physicists, chemists, and mathemati-

cians. The information would be of inestimable value to anatomists, physiologists, surgeons, and, most of all, dermatologists.

Comprehensive and quantitative descriptions of the skin would certainly provide a whole new range of knowledge and technology applicable to both normal and diseased skin. To the extent that lesions of the skin and other organs can be described and identified clinically on the basis of objective measurements, precision in diagnosis and recognition of fundamental pathologic processes could be improved.

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