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Physiology of the skin

George William Thatcher
University of Nebraska Medical Center

PHYSIOLOGY OF THE SKIN

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GEORGE W. THATCHER

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INTRODUCTION

The skin is a mixed tissue. The epidermis is derived from the ectoderm; from the mesoderm are derived the connective tissues, the cutis (on which the epidermis rests), and the blood and lymph vessels; the nerves are again of ectodermal origin. The avascular epidermis derives its nourishment from the cutis. Biologically, therefore, epidermis and cutis belong together.

In the fully developed epidermis we distinguish five layers which, biologically, represent different stages in the development of the epithelial cells. The lower stratum germinativum and stratum spinosum are water-rich and gradually pass over into the drier stratum granulosum and stratum lucidum to end in the fifth and outermost horny layer. As the growth of these cells proceeds from below, this lower part is the most vital, a fact expressed histologically by its marked ability to take up dyes. There are no vessels in this superficial skin, the cells being bathed in a lymph which circulates in the spaces between the epithelial cells. These intercellular spaces constitute a heavily branching network of canals which communicate directly with the lymph channels of the cutis, (Hudack and McMaster, 1932).

These cells react to stimuli thru a relationship between the state of excitation of a cell and its permeability. Increase or decrease in permeability parallel activity and rest in a cell. Such changes must obviously favor the entrance or exit of materials from the cell thru which the activity of its ferments may be altered. Substances produced in the skin may, therefore, pass into the lymph and blood, and so affect the whole organism, (Memmesheimer, 1926).

The blood vessels of the intigument are of importance. The papillae carry a subpapillary capillary net consisting of delicate anastomosing vessels mainly running parallel to the surface of the skin. As these are tortuous and branching, they have great surface. This capillary system coalesces, forming descending veins. The venous blood returning from the capillaries passes thru four nets. The first and second lie immediately under the surface of the papillae but still outside the subpapillary arterial net. The third is found in the lower half of the curtis, and the fourth at the junction of the cutis with the subcutis. A coarser arterial network, still capable of being affected mechanically, parallels the subpapillary vessels. A heavily branching set of blood vessels, thru which there moves a large volume of blood readily accessible to the effects of stimulation, is, therefore, found immediately under the epidermis, (Carrier, 1922).

The vessels of the skin react to various stimuli with either an increase or decrease in caliber. The number of capillaries which becomes patulous in different organs, increases and decreases with the activity and rest of that organ. Since endothelial cells of the skin, because of their position, are readily accessible to stimulation, it is reasonable to suppose that they must be of large significance in the defensive mechanisims of the organism. These cells constitute, moreover, a part of the reticulo-endothelial system to which importance has been assigned in the defense against infection. Observations on human beings show that changes in the reticulo-endothelial system greatly affect the course of infections, (Kingery, 1926). Both increase or decrease in the cellular or humoral defensive reactions have been observed. These reticulo-endothelial reactions occur in all organs, and the importance of skin rests in the fact that this constitutes a superficial, and, therefore, readily accessible organ.

Scarcely any organ is possessed of as highly developed and differentiated nerve mechanisms as is the skin. The effects of all kinds of stimuli on these mechanisims must obviously be large. Over the sensory tracts innumerable nervous centers and internally situated organs may be called into play, (Ozorio, 1924). Reflexes initiated in one skin area may, thru the central nervous system affect another. The stimulation of one skin area with its vasomotor effects may thus express itself not only locally, but in other regions of skin or mucous membrane, and may also serve as a regulative or stimulative center for inner secretion. However, attempts to diagnose gastric carcinoma and gastro intestinal disease by skin studies have been quite unsuccessful, (v Groer, 1925; Brandenberg, 1926).

The skin frequently serves as an index of endocrine function, (Becht, 1921). Addisons Disease, Simmons Disease, change in age, and physiological conditions as seen in pregnancy are but a few wxamples, (Bucky, 1936). Coordination of movements and sense of perception are directly dependent on the skin (Ozorio, 1924).

The skin as an organ of the body is subject to the same laws of health and disease as those that govern the other organs, the only difference being its exposed and external position, (Galloway, 1921). It receives its nourishment from the blood stream, and is therefore, affected much as any other organ might be from anomalous conditions as to quality and quantity of the constituents of this fluid, (McGleason, 1920). Not only is the skin affected by nerves, but is also amenable to blood borne conditions as seen in thyroid, bacteremia, erythemia multiforme, dermatitis herpitiformis, and a host of other conditions, (Engman, 1919). Before considering the various functions of the skin *per se*, a consideration of some of the general chemical physical properties of the skin is in order.

Chemico-Physical Properties

The recent work done in the nature of the skin has brought forth a vast fund of information leading one into the fields of physics and chemistry. For some time it has been known that the skin has a circulatory system consisting of blood and lymph vessels. Only recently has it been demonstrated that there exists an intracellular dermo-epidermic circulation (Pautrier, 1928). Dr Pautrier demonstrated this by means of three complicated but interesting procedures. First, by using the silver reduction of melanin, he showed that the Langerhans cells interposed between epidermis and derma constitute the site of two currents of pigmentary substances; one which runs from the derma toward the epidermis (Chromagenous) and the other from epidermis toward and into the derma, pigment being produced by the Langerhans cells, and distributed to the dermic cells which they color. Secondly, he stained fats and the esters of cholesterol in xanthoma with Scarlet R. From this he concluded that there exists a cellular network which, through the medium of connective tissue cells, connects the vascular endothelium with the Langerhans cells, and these cells in turn with the epithelial-cells. Not a single link is missing in the endothelial-Langerhans chain. Thirdly, he demonstrated the dermo-epidermic circulation by the staining of ferric pigment (hemosiderin) in Schanberg's Disease with potassium ferrocyanide and muriatic acid.

In edema, the familiar principles of osmotic pressure are in operation. The importance of the skin becomes apparent when the extravascular physical factors in edema are considered. There is the effect of tissue pressure in regulating edema. As greater volumes of edema fluid gather, the absolute value of the tissue pressure increases, attaining extremely high values. The skin *per se*, when stretched, exerts a counter pressure, contributing to tissue pressure, tending to limit edema formation. This counter pressure is maintained by the fibrous connective tissue of the corneum, with layers of epidermis, contributing a lesser but significant part. The epidermis inhibits water loss from the blood vessels in that it inhibits the loss of fluid from the tissue outside, and in turn from the vascular system by preventing diffusion and oozing of water into the atmosphere. The very thin layer of corneum prevents fluid escape from the body, and thereby aids in maintenance of the proper electrolyte balance. In the normal physiological state, little water diffuses through the epidermis of the skin. (Burch and Wisnor, 1919).

With the development of improved methods of chemical analysis, there has been a marked increase in the knowledge of the chemistry of the skin. By taking suitable samples, and following the procedures of differential staining and qualitative analysis, and also microchemical procedures it has been possible to demonstrate the presence of various enzymes, minerals, lipids, and other substances.

It has been shown that the skin contains several enzymes. There is protease and peptidase. Lipase and cholesterol are also present, and are of great importance in the skin's resistance to tuberculosis and bacterial infection. There is also catalase, more abundant in fetal skin than in adult. Normal healthy skins have more catalase than do the pathological. The skin also contains diastatic ferments, (Sexsmith and Peterson, 1918). The enzymes have an important function in relation to atrophy and autolysis of tissue. There are two groups of enzymes, the one acting in an acid medium and converting the acid tissue proteins into primary clevage products; and one which attacks only the primary clevage products of proteins producing the amino acids. Any increase in acid production in cell or tissue beyond the capacity of the buffer mechanism to dispose of immediately tend to produce atrophic changes, (Levine, 1921). Amylase, trypase, and lipase occut in as high concentrations as are found in the liver, (Rudy, 1934).

Within the subcutaneous layers fat is found, mostly in the form of triglycerides of stearic, palmitic, and oleic acids. There are also smaller amounts of the more unsaturated acids and various sterols, including cholesterol, ergosterol, and the lipochromes, the latter being the substance which gives fat its yellow color, and sterol esters, (Engman and Kooyman, 1934). Within the epidermis there are also phospholipids and fatty acids. The the eccrine sweat glande there are small amounts of lipids, and within the apocrine glands there are appreciable amounts of free fatty acids. The sebaceous glands excrete a variable amount of different types of lipids. There is an important relationship between skin lipids and vitamins. Vitamin D is a sterol-like compound which can be formed by the action of ultraviolet light on ergosterol or cholesterol, (Lucas, 1931), and functions as a catalyst for phosphorylization and for the mobilization of calcium, thus affecting the cellular permeability of the skin, (Rosenheim and Webster, 1927). Vitamin A is formed directly from carotene, and is an alcohol and a lipochrome, (Lanc, 1924). It is apparent that fat plays a role in the cornification and keratinization of the skin, but more about this is reserved till later.

There are a number of important chemical constituents which should be considered. The stratum corneum of the human epithelium contains, according to Wilkerson and Tulane, (Wilkerson, 1935; Wilkerson and Tulane, 1939):

1. Nitrogen, refered to as total nitrogen. It represents 15.09% and is calculated on an ash-free basis. This nitrogen occurs as acid soluble humin nitrogen-2 (11%) and amid ammonia nitrogen (3.6%) represented by that precipitated by phosphotungstic acid and that remaining in the filtrate from precipitated bases.
2. Cystine, 2.31% to 2.38%. The amount of Cystine varies, and depends on the state of nutrition of the individual and the presence of debilitating disease.
3. Tyrosene, 5.0%
4. Tryptophane, 1.49%
5. Basic amino acids
    a) Histidine, 0.57%
    b) Lysine, 3.08%
    c) Argenine, 10.01%

    These basic amino acids occur in molecular ratios of 1:5.6:15.1 respectively.
6. Total sulfur, 1.09%, which occurs in cystine and

methionine, 55.96% and 48.62% of the total sulfur respectively.

7. Methionine, 2.47%.

The keratins of ectodermal tissues have a similar molecular pattern, and may be defined as proteins which are resistant to digestion by pepsin and trypsin, are insoluble in dilute acids, dilute alkalies, water, and inorganic slovents, and which, on acid hydrolysis yield such quantities of histidine, lysine, and arginine that the approximate molecular ratios of these amino acids are respectively 1:4:12, (Block and Vickery, 1931). The process of keratinization represents the result of the incorporation of the cystine nuclei with the primary cell-forming materials. An increased keratinization is accompanied by an increased cystine incorporation and a decreased methionine content. Since cystine appears to be incorporated at the expense of methionine, it may be reasoned that the skin is less keratinized than the hair and the nails which have a very low methionine content, (Wilkerson and Tulane, 1939).

The skin is also possessed with certain physical properties which are of great importance in the functioning of the skin. Like every other organ of the body the skin has a computable pH. The acidity of the skin surface is a function of the keratin layer, (Goodman, 1943), and depends upon the thickness of the integument and upon several other factors to be mentioned anon. The closer the layer of the skin covering is to the underlying tissues, the closer does the normal pH approximate the pH of the blood (7.3-7.4). The cutis is more alkalin than the superlying epidermis. The pH of the surface of human skin is 5.3, and constitutes an "acid coat" which resists invading organisms, (Goodman, 1943). Sharlit and Scheer (1923) determined the pH of cleaned skin to be 5.5, while Yamasaki (1924) found the pH of water extracts of the skin to be alkaline, 7.1 to 7.5. The normally intact skin tends to have a lower pH at the surface and in the basal layers of the epidermis than in the deeper portions of the cutis. The surface of the skin also tends to be more alkaline in those areas in which the evaporation of sweat is retarded, (Pillsbury and Shaffer, 1939). It is to be noted that the outer layer of the skin is truekeratin, is amphoteric and therefore capable of ionizing both as an acid and as a base, (Wilkerson, 1934). The skin also has a definite buffer action, and is able to withstand solutions the pH of which ranges from minus 2 (three times normal HCl) to pH 12.6, (Pillsbury and Shaffer, 1939).

There is a wide variation of pH of the skin, being dependent on a number of factors. On the exposed surfaces, the pH tends to be lower than on the covered areas and body folds. The flexor surface of the forearm averages 5.1, the extensor surface, 5.3. The flexor surface of theindex finger 5.4, groin, 5.7, axilla 5.8, and the fourth interdigital space of the foot, 6.5, (Pillsbury and Shaffer, 1939). The hydrogen ion concentration also depends on the intactness of the keratin layer. When the continuity of the horny layer is disturbed, or the evaporation of sweat is delayed, the reaction of the skin surface is changed. This is apparent when one considers that intertriginous areas show a lowered hydrogen ion concentration. Visible perspiration tends to raise the pH of the skin surface, and sweat, on standing, and evaporating, increases the acidity, (Levine and Slivers, 1932). Skin acidity depends chiefly on sweat. Areas free from perspiration, or where free perspiration is possible are more acid than areas where evaporation is slower. Heat sweat has a pH of 5.73, work sweat 6.4. The acidity of sweat from covered parts is slightly higher than from uncovered, (Talbert, 1919). The evaporation of sweat produces an increased acidity, and a delayed evaporation interfers with the normal acid reaction of the skin surface. Evaporated sweat, thru its acidity, seems to act like a protective covering for the skin against bacteria, (Brill, 1928) The presence of acids; acetic, proprionic, caproic, caprylic, lactic, and ascorbic also serve as natural protection against invaders, (Bernstein, 1942). The high acidity in areas of free perspiration is due to the concentrations of fatty acids, and a lowering of the alkalinity results fron the decomposition of hydrated keratin,(Bernstein and Hurmann, 1942). The acidity of the skin also varies with temperature, acidity increasing or decreasing with a respective rise or fall in temperature, (Bazett, 1928).

The normal acidity of the skin is reduced when formation of compact scales, atrophy, or other degenerative alterations prevent the skin excreting sweat. For example, myxedema and senile atrophy show low figures all over the body, (Bernsteinand Haumann, 1942). In acute eczymatous conditions the hydrogen ion concentration of the skin surface is lowered. The pH is slightly above or below the normal point. The reaction of the skin surface in erythrodermia is markedly to the alkaline side, (Levine, 1932). Inflammation, icthyosis, maceration and seborrhea also increase the pH, (Bazett, 1928; Pillsbury and Shaeffer, 1939).

The acidity of the skin also varies with the histo logical layers. The epidermal cells are acid. There is an alkaline reaction when the papillary bodies are reached. The cutis is alkaline, and the basal layer is the most acid, with the acidity gradually decreasing until the horny layer is reached where the acidity becomes marked. The acidity of the basal layer is to be explained by the fact that where metabolism is most active, more acid waste products are produced. The horny layer is highly acid because the cells are dead, (Levin, 1932).

Another physical phenomenon of the skin is its electrical resistance, a factor influencing many of the skin's functions. Changes in the resistance of the skin are caused by the unequal tension exerted by the vascular loops in the corium of the epidermis where they contract or dilate, (Densham, 1927). The measurement of the electrical skin resistance is one of the most sensitive methods of examination of the vegetative nervous system. The immediate changes in skin resistance in states of emotion, sleep, and stupor are outstanding examples. Some information may also be gained as to the state of affairs in the central nervous system and the endocrine system, (Levine, 1933). The sympathetic sudorific mechanism is known to be the source of an electric potential and resistance response of the skin. There are two mechanisms represented and the response is held to be a unitary response. Experimental results suggest that the b potential is connected with a diffuse type of sympathetic activation, while, the a potential appears nonsympathetic. Evidence for this consists of the independent variation in amplitudes of the a and b potentials, their apparent separate occurrence, and the apparent dependence of the b deflection on an intense or an apprehension producing stimulus. The occurrence of summation of action potential has been held to indicate secretion rather than excitation in sympathetic and para sympathetic mechanisms, and on this basis the occurrence of summation in both a and b potentials would favor the idea of two separate reacting mechanisms. The occurrence of a decrease of impedence with either a or b potentials is evidence that both mechanisms involve tissue permeability, (Forbes, 1936).

The re$istance of the skin varies from day to day and from individual to individual. Sweating, body temperature, and vasomotor changes are usually assumed to control skin resistances. There are numerous other factors such as:

1. Water content of the epidermus, the less water the greater the ristance.
2. Mensturation affects water retention, i. e., there is a loss of water.
3. Adrenals govern sodium metabolism and cortical atrophy produces an increased skin electrical resistance.

4. The more Iodine in the skin, the lower the resistance, (Landis, 1927).

The wide variations in electrical resistance are not the result of sweat glands or vasomotor activity alone, but also depend upon the content of extracellular water and electrolyte balance which may be controlled by estrogenic, adrenal cortical harmones and other steroid harmones with water retaining properties, (Hemphill, 1942).

The skin has one other physical property of great importance, the response to irradiation. The response to x-ray and radium has been adequately described, and does not fall within the confines of this paper. There is a response to ultraviolet light which is very interesting. It has been pointed out that pigmentation is an almost universal reaction to light, (Fleure, 1926). Ultraviolet light produces vasodilitation and also increases metabolism. This, in turn results in an increase in vessel wall permeability, an acceleration of keratinigation, and an increased production of pigment. The mechanism of these reactions is not too clear. There is a photo chemical reaction produced when light energy is absorbed. The absorption of rays by liming protoplasm produces toxic reactions brought about by the tyrosin and phenylalanine radicals of the protein molecules. The protein solutions are made less soluble, and oxygen is converted to zone.

The cells in the germinative layer form a pigment and also an oxidizing ferment which reacts with "some substance (?)" brought to the cell by the blood stream and results in the production of pigment. Sunlight and ultraviolet light increases this reaction, (Lane, 1924). Pigmentation *per se* is to be discussed later in more detail.

The transmission of infra-red light has occupied the attention of numerous investigators, and it seems that the most penetrating rays do not pass very deep. About 95% are absorbed within the first two millimeters of the surface, and 99% within three millimeters of the surface. The use of dead skin in experiments on infra-red transmission has been shown to lead to too high, rather than too low transmission values. The heating effect of infra-red radiation is exerted principally on the body surface, and whatever therapeutic effect is obtained by such radiation is due to this local effect and not to deep penetration of the rays which is shown to be negligible in amounts. Photography of the human body in infra-red light, while yielding detail not obtainable by ordinary photography, will not yield pictures of structures more than a few millimeters under the surface, and due to scattering, will not give sharp detail. The absorption spectrum of normally wet skin is essentially that of liquid water, and upon drying, other absorption bands not due to water become evident, (Hardy, 1936).

The ~~varied~~ functions of the skin have been adequately summarized and generalized in the numerous text books of Physiology, and only those conclusions not described in these books will be amplified in this paper. The functions of the skin may be grouped under three main headings, following the suggestions of Dr. A. J. Hall, (1921).

1. Those functions pertaining to the exterior, and including:
    1. Protention
    2. Reception of nervous stimili
    3. Self-sterilization
2. Those pertaining to the interior, and including:
    1. Secretion and excretion
    2. Pigmentation
    3. Absorption
    4. Sensitization and immunity
    5. Storage of water, salts, minerals, and sugar
3. Those pertaining to both, and including:
    1. Heat regulation
    2. Respiration
    3. Metabolism

Protection

Due to the insensibility and relative impermeability of its corneus layer, the epidermis serves as a defense against physical, chemical, thermal, actinic and other injurious agents and micro-organisms, (Hall, 1926). It acts as a barrier, to a certain extent, against the absorption of most substances. It controls surface evaporation and prevents the entrance of undue moisture. Due to its pigment content, the epidermis protects the underlying tissues from excessive radiation. An additional protective feature is the hair, which, for example; serves to protect the scalp from exposure to heat and trauma. In fine, the skin serves as a shock tissue, (Coca, 1929). Urticarial leseons may be regarded as the expression of a general mechanism of defense in the skin against injuries of all kinds. It is the result of purely physiological processes. (Grant, 1926).

Reception of Nervous Stimuli

The main function of the sensory nerve endings in the skin is the perception of heat, cold, touch, and pain; but it is still uncertain which of the nerve endings serve for tactile, thermal, or pain sensibility. Cutaneous sensation is not uniform on the whole surface of the body, but is limited to very small discrete areas called temperature, and/or touch, spots, (Fleure, 1926).

By means of the tact le sensibility, the size form, texture, and other characteristics of bodies can be made known. The number of "touch spots"varies greatly in different regions of the skin. Fingertips, lips, nose, and tongue, have been found to be the most sensitive areas of the body. Change in pressure at sufficient time intervals forms the adequate physiologic stimulus for the touch spots. Uniform and continuous stimulation soon becomes ineffective, (Engmann, 1919(.

In testing the thermal sensibility of the skin, hot and cold spots are distinguished. Their distribution in different individuals varies considerably. Generally, however, they are less numerous on the face and hands than on the tongue. The thermal receptors do not respond to mechanical stimulation, but temperatures above 50 degrees C. usually give the sensation of pain. If a punctate hot stimulus is applied to a "cold spot", it can elicit a feeling of cold - the so called paradoxical cold, (Hall, 1921).

The temperature spots respond only to relatively intense thermal irritation, while some other nerve endings probably subserve the recognition of intermediate stimuli. A temperature change of only 0.003 degrees C. on the warm side is sufficient to elicit temperature sensation; the threshold for cold is about five times greater. The thermal sensibility is diminished when the skin is very hot or very cold. Like all sense organs, thetemperature receptors adapt themselves to continuous stimulation. Thus, even a comparatively hot or cold stimulus ceases to elicit sensation when applied continuously for a sufficient length of time. The exact mechanism of temperature perception is not known, (Muller, 1925).

The sensation of pain can apparently be elicited from any area of the skin. The actual mechanism of pain production is aslittle understood as that of temperature perception. It is now thought that the injured epithelial cells release some chemical substance which stimulates the sensory nerve endings. The highly complicated subject of nerve conduction does not fall within the scope of this writing. Suffice it to say that special nerve fibers are now assumed to convey the sensation of paid to the spinal cord, and that the thalamus opticus in the mid brain is regarded as the most important center for the recognition of pain sensation. The sensation of tickling has been attributed to the reaction of pressure points, that of itching to the pain points, providing the stimulus is delicate, (Kingery, 1926; Wolff, Hardy and Goodell, 1940). If skin response is under central cortical control and autonomic control, stimuli intensity can be adjusted in such a manner as to obtain equal subjective experiences. Simultaneous measurements of pain threshold and skin resistance should furnish a means for differentiating between autonomic effects, and those involving higher centers. Skin resistance to pain threshold is of value in differentiating various aspects of drug action. For example; Morphine increases the pain threshold, reduces the reaction to a recognized pain , and reduces the "alarm reaction", (Andrews, 1943).

Self-Sterilization

For some t me it has been observed that the skin has certain self-sterilizing powers, but the exact mechanism thereof was a matter of speculation. Self-sterilization is accomplished rather rapidly - 73% in ten minutes, and the efficiency decreases as the task continues, (Cornbleet, 1923). There is a wide variation in self-sterilizing properties, depending on the local areas. Areas in the immediate vicinity of the nails are less efficient because of dirt and constant trauma. Folds of the sk n subject to constant moisture are inefficient at destroying bacteria. This may explain why perleche often tends to be symmetrical, (Cornbleet, 1923). Partial denudation of the epithelium, the presence of yeast infections, and psoriasis inhibit the skin's destruction of bacteria. In fact, the self-sterilizing capicity is still further depressed when there is any skin pathology, (Cornbleet, 1923).

The skin's ability to destroy bacteria is enhanced by exposure to ultraviolet light, be it sunlight or ultraviolet light <u>per se</u>, (Bryan, 1933). The mechanism of this is to be found in the action of ultraviolet light on skin lipids. Many oils which normally will not kill bacteria are bactericidal after exposure to ultraviolet light or after ozonizarion. Not only are the irradiated oils bactericidal, but their vapor inhibits bacterial growth and fogs photographic plates. These acquired propert es are due to the oxygen attached to the molecules of oil during irradiat on and subsequently released in the active state, (Stevens, 1937). Since it has been shown that other fats and oils become bactericidal when irradiated, it is reasonable to assume that skin lipids are bactericidal by virtue of the same mechanism, because the lipids have the same properties of other irradiated fats and oils. Irradiation increases the active oxygen content of dried skin markedly, but little increase occurs if the lipids have heen extracted. Although the normal lipids extracted from the skin contain some active oxygen, the active oxygen content is much increased by irradiation. Vapor from skin lipids also retards the growth of hemolytic streptococci, and when emulsified in salt solution, the irradiated lipids kill hemolytic streptococci promptly in comparison with emulsions of lipids which have not been rradiated. The addit on of neutralized cysteine hydrochloride to the emulsions of the lipid, normal or irrad ated, prolongs the life of bacteria suspended in the emulsions. This protective effect is due to the reducing action of cysteine. Normal nonirrad ated lipids, extracted from the skin under conditions permitting oxidation, kills bacteria more quickly than under conditions which inhibit oxidation, (Stevens, 1936). It should be noted, however, that intense actinic illumination produces a drop in the sympathetic tonus 24-48 hours later, a fall in blood sugar level, a change in catabolism of purins, and a rise in tyrosin in the blood. There is also a proteolysis and splitting off of ring compounds from the protein molecule. These factors are thought to be of importance in the skin's bactericidal properties, (Memmsheimer, 1926).

A second factor contributing to the self-sterilizing properties of the skin is the acid p H. Hall and Fraser (1922) were of the opinion that there is a possibility of lactic acid being a factor in promoting infections. Levine and Selvers (1932) found that the acid reaction of the intact stratum corneum has the ability to disinfect itself rapidly and efficiently, and that greasy substances on the skin inhibit this disinfecting property. Cornbleet (1933) announced that the effect of the acid corneous layer in resisting infection by means of its acidity _per se_ is highly theoritical and unproved. He further showed that sweat is a good culture medium for yeasts and staphylococci at p H from 3 to 8. Thus the matter now stands awaiting further investigation.

Thirdly, it has been advanced that the skin has certain bacteriolytic substances which are products of the normal metabolism of the skin. The presence of such substances has not been demonstrated, (Hill and White, 1933).

Fourthly, skin infections are often associated with hyperglycemia, and a lowered tolerance for carbohydrates, (Gettler, 1918). An increase in the sugar content of sweat may lead to conditions more favorable to bacterial growth (Usher, 1929).

The ingestion of sugar has a powerful dynamic action on the rate of self-sterilization, and the curve of this property runs parallel to the curve for the blood sugar level. The curves for the self-sterilization and blood sugar levels after a sugar tolerance meal are both biphasic with first a rise and then a depression. A similar curve of different dimensions is also found after non-specific therapy with the end results reversed, however, the rate of self-sterilization is not dependent on the absolute height of the blood sugar, since one finds similar values for sterilization rates in normal persons and in diabetic patients witha very high figure for blood sugar. The changes in the skin's ability to inactivate micro-organisms are related to the direction of amplitude in the sugar level curve from a fasting level. There is a marked depression in the self-sterilizing abilities of the skin coincident with the dip below the fasting level late in the sugar tolerance curve, (Gettler and St. George, 1918). The degree of retardation appears to be related to the sluggishness with which the sugar curve returns to the fasting level. Diabetic patients are to be regarded as more easily infected because their sugar tolerance curves take longer to return to the fasting level, (Greenwood, 1927). Diabetic persons also vary in the ease with which their blood sugar levels are raised or depressed. Some have more prolonged changes than others. The phase of their curves lasts longer, produces a more prolonged depression of the capacity for self-sterilization and thus gives the micro-organisms a longer time to gain a foothold beyond the skin's primary defense mechanism against infection. In a similar way, certain normal persons of an unstable type are also more liable to infection. Their blood sugar curves are not so well poised between the narrow limits found in most persons, and their directional change in amplitude of the sugar tolerance curve is more sluggish. It follows, then, that persons who are prey to cutaneous infections should not eat a large quantity of easily assimilable carbohydrates at any one time.

Since there is comparatively less carbohydrate tolerance in the early morning before the more intense metabolism develops later in the day, those subject to cutaneous infections should consume the bulk of their carbohydrates at the later meals, (Cornbleet, 1932).

The most recent investigations indicate that the mechanism of self-disinfection of the skin is a result of the long chain of fatty acids and soaps. The fatty acids are active constituents which are found in sweat, as lactic and cytric acids, and the fatty acids up to caprylic. They are also found in the sweat glands, especially the apocrine glands of axilla-perineum. Sebum also contains long and short chain fatty acids and their esters. Cystein and blood inhibit the streptoccicidal activity of skin fats and certain fatty acids. Ultraviolet light increases this activity as previously pointed out. The mechanism of the sterilizing powers of fatty acids and soaps is the result of their surface tension lowering power, (Burtenshaw, 1942).

Secretion and Excretion

Although very simple in anatomical structure, the sweat glands have to cope with a task hardly less multiple and variegated than that of the most complex glands of the body. As organs of excretion, the sweat glands are functionally interrelated with the kidneys, and to a lesser degree also with the gastro-intestinal tract and the lungs. They are thus concerned with the maintenance of the normal water, salt and acid-base equilibrium of the body. Sweat is composed largely (98-99%) of water; is colorless, and has a specific gravity of 1003 to 1008. It is similar in composition to urine, containing Na Cl, sulphates, phosphates, urea, uric acid, lactic acid, creatinin, and indican ammonia, (Peck, 1939). It also contains fatty acids. The sodium chloride content of sweat, which is normally about 0.3%, increases in excitementand decreases again if the excitement is of comparatively long duration, (Kittsteiner, 1911). Under normal conditions sweat is acid, but after perfuse persperation, its reaction becomes neutral or alkaline. Thermal sweat may have a fungistatic and fungicidal property at a p H below 7, (Peck, 1939). The fungicidal properties are due to its content of acetic, propionic, caproic, caprylic, lactic and ascorbic acids, (Way and Memmesheimer, 1936 and 1938). The relative excretory importance of the sweat glands is demonstrated by the fact that in individuals doing strenous work at high temperatures, the nitrogen excretion thru the skin has been found as high as 12% of the total nitrogen excreted. Excessive sweating in hot weather may lead to a marked depletion of sodium chloride in the body with resultant very painful cramps of the sheletal muscles. The urine in such cases shows only minimal concentrations of sodium chloride. Vitamin C has also been shown to be excreted in sweat. It has been suggested, therefore, that prolonged sweating in individuals who are continuously exposed to high temperatures, such as , glass blowers, miners, etc., may cause Vitamin C defficiency. However, in view of the minimal amounts of vitamin C that are excreted in the sweat this contention can hardly be accepted. The close reciprocity between sweat glands and kidneys is also evidenced in renal incompetence. In uremia, the excretion of sodium chlorides and urates in the sweat may be increased to such an amount as to cause visible deposits of these salts on the skin, (Lane, 1924).

Many chemicals introduced into the body may be partly eliminated by the sweat glands. Iodine, bromine, chlorine, sulphur compounds, arsenic, phosphorus, ether, tars, turpentine, musk and copaiba are some of the substances that have been observed in sweat. Such pathologic secretions may sometimes give rise to chemical symptoms. Arsenic and phosphorus, for instance, can account for offensive odors. Appearance in the sweat of constituents of normal and decomposed food products has been considered as possibly responsible for pruritis, (Way, 1931).

It is customary to distinguish between sensible and insensible perspiration. The term "sensible perspiration" indicates the appearance of sweat on the skin in the form of visible droplets. The term "insensible perspiration" is usually taken to denote the invisible elimination of fluids from the body. However, the distinction between these two processes is a very artificial one. It depends largely on the skin in the form of invisible vapor. Furthermore, evaporation of water takes place, not only through the sweat glands, but also by direct permeation of tissue fluid through the epidermis. Lastly, the term "insensible perspiration", as used by physiologists, implies not only the evaporation of water, but also the loss of carbon dioxide through the skin and lungs.

The activity of the sweat glands can be influenced by many heterogeneous stimuli. Sweating on thermal stimulation is obvious. The reaction of the sweat glands to direct central or nervous stimulation is exhibited; for instance, in emotional sweating,

sweating or painful cutaneous irritation, or ingestion of strongly spiced foods as well as in experimental electrical stimulation of the secretory nerves. Drugs may stimulate sweating in different ways. Some, such as pilocarpine, muscarine or physostigmin may act peripherally on the endings of the cholinergic nerve fibers that supply the sweat glands. Reversily, atropine paralyzes them. Strychnine and camphor stimulates the centers in the spinal cord. A third group, to which the anti pyritics belong, acts on the higher centers in the brain. The precise nervous control of the sweat glands is still a matter of much speculation and need not be herein considered.

The secretory product of the skin is sebum which consists chiefly of esters of fatty acids and higher alcohols, and a smaller amount of triglyciricles, (Rimington, 1934). It keeps the integument soft and supple, preventing the formation of fissures and the consequent entrance of bacteria into the skin. In addition, sebum renders the skin less permeable; it impedes too rapid an evaporation of sweat and in that way helps to conserve heat. This is borne out by the distribution of the sebacious glands; for where the subcutaneous fat deposit is the thinnest, as on the lips, nose, scalp, and on the suprastemal and supravertebral lines of the chest and the back, it is compensated for by, a denser aggregation of sebaceous glands.

The secretion of sebum is controlled by external as well as by internal factors. The latter are seemingly of less importance, but it has been found that a rise in the external temperature is accompanied by increased fat secretion. No measurable influence could be induced by body exercise, sweat secretion or the administration of pilocarpine, atropine, or thyroid extract.

Sebum secretion is not continuous, but stops when the skin surface has reached a certain degree of saturation with sebum. Secretion occurs when the sebum is removed by washing or some other procedure. This limit of saturation differs individually, but is said to be rather constant in the same person. The actual amount of secreted sebum averages from about 1 to 2 grams daily, (Lane, 1924).

A number of local and systemic factors have been investigated as to their relation to the secretory activity of the sebaceous glands. There is an interesting connection between sebum secretion and age and sex gland activity. The formation of the fital vernix caseosa is the result of stimulation by hormonal substances from the mother. After birth, the infant's sebaceous glands become quite inactive, to assume greater importance only at the time of puberty, for then the hormonal stimulus sets in once again. During the onset of senility, there is a period when the sebum is markedly enhanced. This occurs shortly before the senile shrinkage of the glands, (Becht, 1921).

Constitutional differences in sebum secretion are often correlated with adiposity and pigmentation. The activity of the sebaceous glands is, as a rule, greater in slender people than in adipose ones, and more marked in brunettes than in blond individuals. It has been observed in diabetics suffering from furunculosis that the sebum secretion was diminished, (Bram, 1928). The same has been reported in experimental bromine acne and in plaques of psoriasis, (Kuznitzky, 1913). The findings in diabetic and experimental bromine acne induced Kuznitzky to suggest that decreased sebum secretion might facilitate infection by either permitting a longer presence of bacteria, or by lack of bactericidal action of sebum. In contrast to this, the secretory activity of the sebaceous glands is increased in acne vulgaris, but in that condition the sebum is abnormally diluted, Kuznitzky (1913) sees in the hypersecretion in acne vulgaris a defense mechanism against the micro-organisms, and explains the usual disappearance of the disease after puberty by the normal more concentrated sebum of adults.

There is no clear cut picture of the exact control the nervous system exerts over the secretion of sebum.

The effect of diet on sebum secretion is interesting. It has been demonstrated that a carbohydrate diet tends to lower the secretion of sebum. Also, the fat taken up in the food appears in the sebum, and an abundant intake of fat consequently increases the total skin fat, (Kuznitzky, 1913).

Pigmentation

The coloration of normal skin depends chiefly on its vascularity, i. e., the presence of oxyhemoglobin and reduced hemoglobin, and on its melanin content. In man, melanin gives the skin a certain protection against the injurious effects of light by absorbing a considerable part of the rays, especially at the violet end of the spectrum, (Edwards, 1937).

The mechanism of pigment formation has engrossed the attention of scientists for a long time, and in spite of painstaking investigations, the subject has not advanced beyond the stage of conjecture. It appears that there are two types of cells - those which produce melanin, the melanoblasts, and those which merely take up the already formed pigment, the melanophores. Cells which are specially endowed with the property of pigment formation are normally found in the epidermal layer of the skin, but not in the corium. The melanin formed in these basal cells is taken up by the melanophores and carried partly into the corium where it is later absorbed, partly toward the surface where, after having been decolorized, it is ultimately cast off together with the horny cells.

There has been considerable speculation as to the possibility of a precursor of melanogen. Recent experimental findings by Rothman (1940) have lent support to the theory that tyrosine may represent that precursor. He shows that the formation of melanin by ultraviolet irradiation _in vitro_ is very slow. He also showed that this reaction is greatly accelerated by the presence of ferrons salts, which would explain the rapid pitmentation that follows the natural irradiation of the human skin. The source of melanogen is obscure.

The conversion of melanogen, the colorless precursor of melanin, into the final pigment is brought about by the oxidizing enzyme in the cell-nuclei of the melanoblast. The exact chemical nature is as obscure as is that of melanogen. It has not been possible, as yet, to isolate either in a chemically pure state. Not much is known about them, other than they are composed of large organic molecules; they contain carbon, hydrogen, and nitrogen, and that these atom complexes apparently have the tendency to bind certain sulphur and iron compounds, e. g., cystine and hematin derivitives.

The regulation of pigmentary changes has been explored quite inadequately. The fact that an excised piece of skin can produce intense pigmentation, shows that melanoblasts can form pigment autonomously. It is certain, however, that other than purely local mechanisms are able to exercise an influence on melanin formation. Hormonal control is indicated by such well-known symptom complexes as those seen in Addison's Disease or in gravidity. Vitamins are likewise reported to have some relationship to pigment formation. Thus, Cornbleet (1937) has found that skin pigmentation is enhanced when the vitamin C reserves of the body are markedly reduced. He contends that the pigment is anchored to vitamin C and is released when the latter is lost. Copper is also associated with vitamin C and melanin in the skin. Copper hastens the darkening and precipitation of dopa by ultraviolet rays. Vitamin C retards this precipitation. The presence of all three makes them sensitive to control, so that the amount of pigment may be quickly changed.

It seems fairly well agreed that the conversion of melanogen, the colorless precursor of melanin, into the final pigment, is brought about by an oxidizing enzyme in the cell nuclei of the melanoblasts previously mentioned. This enzyme has been called "dopa" or levo-di-oxyphenylalanine. When skin sections are treated with the dopa oxidase, the dopa is transformed by oxidation in the melanoblastic cells into a dark insoluble substance. This is called the "dopa reaction", and is positive in pigment producing cells of the epidermus, and also in the cells of benign and malignant melanomas,, and other disorders, (Arnow, 1937).

Vitamin C and dopa absorb selectively the erythema-producing ultraviolet rays; the power of absorption increasing when the same concentrations and thickness are used. Tyrosine subjected to ultraviolet radiation and dopa possess greater power to absorb actinic rays than the same non-irradiated substances, (Cornbleet, 1937).

Absorption

There are a number of substances which the skin absorbes with varying degrees and ease. By and large, the intact skin offers more resistance than does an abraded skin. Any abrasion, no matter how slight,involves the passage of material into skin lymphatics. The lymph flow is relatively rapid, and "local" lesions are much less local than is usually considered, (Hudack and McMaster, 1932).

One substance absorbed by the skin is water. The amount is not large, but it is significant. Recent investigations (Hallay, 1942) show that, not only can water be "drunk" by way of the skin, but a survivor of a wrecked ship may be able to quench thirst by immersing the body in sea water without immediate incorporation of the Na Cl contained in it.

Oxygen is also absorbed by the skin, and will be discussed in more detail under Respiration. Suffice it to say here,that studies of oxygen consumption of small particles of healthy and pathological skin show that there is a parallism between the rate of oxygen consumption and the sensitivity to roentgen rays, (Gans, 1923).

Vitamin D is readily absorbed by the skin, and seems to be independent of the source-natural or synthetic. It may be absorbed when ergosterol is irradiated, or by application of ointments and creams - ex viosterol, (Hume, Lucas, and Smith, 1927). The action of viosterol by inunction appears to be by direct molecular absorption, rather than by secondary irradiation, (Astrow and Morgen, 1935). Vitamins A and C are also absorbed through the skin, (Eller and Wolff, 1940).

Through the skin numerous drugs may be absorbed, affecting the skin as well as other organs of the body. Ions may be introduced into the skin by simple ion transportation. This simple transport is complicated by an electro-osmotic flow which may increase, decrease, or inhibit the transport of a given substance. Electro-osmotic transport will in general, act independently of the iontophoretic transport. It should likewise be noted that the pores of the skin bear electric charges. It becomes evident, then, that in absorption of drugs through the skin, the electrical charge of the skin as well as that of the drugs themselves become important, (Abrahamson, 1938).

Volitale oils are readily absorbed through the skin and are often successfully used as vehicles to introduce into the body various substances, (Macht, 1938).

Iodine and Bromine are absorbed through the skin. Kollmer (1916 and 1917) showed that not only are iodine medeciments absorbed per skin, but that they will yield a false positive in serological tests for syphilis. Nicotine is readily absorbed through the intact skin and mucous membranes. In pathological states, the absorption is markedly increased,(Macht, 1938). Insulin is absorbed in very slight amounts through the intact skin. With slight abrasion, appreciable amounts may be absorbed, (Burger, 1936; Major, 1937).

Fats permeate the skin, and do so in large measure along the hair shafts and into the oil gland ducts. Liquid fats permeate more rapidly than solid fats, with animal fats showing the greatest depth of penetration. Most of the fats show optimum penetration between four and six hours after application, and after six hours, the quantity of fat in the deeper tissues appears to diminish, (Eller and Wolff, 1940).

Androgens and estrogens are absorbed readily through the intact skin when applied in a solution or ointment, (Eller and Wolff, 1940).

By cutaneous application, hormones can cause systemic effects similar to those observed after ingestion or injection of these substances. In some instances, the effects are even greater by percutaneous absorption, (Eller and Wolff, 1940).

Immunization

The reactions of the skin to various agents have brought forth much speculation and little fact. There are three types of reactions which may be grouped as follows, (Kòllmer, 1917):

1. True anaphylactic reaction due to the inter-action in the skin of specific protein antigen and specific antibody.
2. Pseudo or nonspecific protein reaction due to the interaction in the skin of general protein substances and non-specific proteolysis.
3. The traumatic reaction consequent to operation; or to the irritant qualities of such substances as preformed bacterial toxins and various preservatives, such as, phenol and tricresol contained in injected material. Clinically, skin responses are used in ascertaining immunity to certain infections (Shick Test): diagnosing disease (Mantoux); and determing susceptibility to various proteins, (Pigott,1926). Kallmer (1917) demonstrated that iodides produce reactions through non-specific and traumatic bases, rather than on specific anaphylactic reaction. He found that some drugs will increase the action of others. For example, KI increases the shick toxin reaction. The mechanism is not known, but probably the non-specific

traumatic skin reactions implicate the proteolytic ferments of fixed tissue cells, leukocytes, and serum which produce from the injected protein and probably from the protein in the patient's own serum a soluble toxic substance responsible, in part, for the reaction in the skin in erythema, edema, and leukocytic infiltration. The iodides probably influence the leukocytes, and facilitate the phagocytosis of foreign injected material, producing a heightened inflammatory reaction analagous to the focal reaction not infrequently, following the administration of a bactericidal vaccine in adequate dosage. "It would appear, therefore, that the oral administration of potassium iodide and to a lesser extent of potassium bromide may increase the phagocytic power of the blood serum for B. Prodigiosis and may have some influenceupon skin reactions by increasing leukocytic infiltration about the injected mass", (Kollmer,(1917).

There is a group of diseases which is characterized by the skin's inability to metabolize proteins. These diseases may be referred to as "protein idiopathies" and include asthma, paroxysmal rhinitis (hay fever), animal sensitiveness, food sensitiveness, urticaria, eczema, ichthyosis, et al, (Freeman, 1926). These protein idiopathies are characterized by a peculiar and specific sensitiveness to one or more foreign proteins. Hay fever is not only a result of a protein sensitization reaction, but such a reaction often produces dermatitis. Protein sensitization is influenced by: (Barber 1921)

1. Heredity.
2. Gastro intestinal disease - frequently influencing the acquired sensitization to food and bacterial proteins.
3. The constitution of the patient, (Murray, 1921).

The part the skin plays in anti-body production has been studied. Anti-bodies may be present in relatively high concentration in tissues which have been locally immunized. Local immunity is thus an important element in the general mechanism of defense. Locally increased resistance to infection may be due in part to a locally increased formation of antibodies. Therefore, local immunization of organs and tissues would seem to be indicated whenever practically possible as a supplement to the methods of general immunization as practiced at present, (Cannon and Sullivan, 1932). This conclusion is the antitheses of that of Muller (1925) who claimed local immunization does not lead to the production of antibodies. Cannon, however, is of the opinion that antibodies are formed locally within the skin, and are products of macrophages.

That the skin definitely is an immunological organ is borne out by three clinical considerations. First, in exanthematous diseases a marked skin eruption has been regarded as a good prognostic sign. Secondly, in syphilis patients with marked primary or secondary manifestations rarely develop nervous or severe visceral involvement. Thirdly, patients with skin tuberculosis rarely develop pulmonary tuberculosis, (Tuft, 1931).

The exact role played by the skin in immunization is not too clear. There is a distinct relationship between skin and the process of immunity, and the skin does have an extremely marked capacity for sensitization and can possibly produce antibodies. It is also known that in alergic diseases, the body forms specific antibodies, and that in certain infectious diseases cutaneous antibody formation may be a means by which immunization of the entire body is brought about. The use of thyroid vaccine seems to indicate the skin has an active participation in antibody formation, (Tuft, 1931).

Heat Regulation

The role played by the skin in the regulation of body temperature may be regarded as one of its most important functions. Variable amounts of heat are constantly produced in the organism as a result of tissue oxidation, chiefly in the skeletal muscles and the great organs such as liver and kidneys. So remarkable is the capacity of the heat regulating mechanism that only in extreme conditions does the body temperature deviate as much as ±1.0 degrees F. from the normal average of 98.6. Slight variations of the physiologic body temperature are caused by such factors as age, food intake, exercise, menstruation, but these are either rapidly adjusted to the normal level or, as in the case of old people and very young infants, constitute a sign of general debility, (Hall 1921).

The heat regulating mechanism is governed by a nerve center situated in the hypothalamic region of the brain. The secretory activity of the thyroid and adrenal glands, and possibly certain products of tissue metabolism, serve as subsidiary mechanisms. This nervous and hormonal control may be regarded as a physiologic factor of heat regulation; it governs the heat flow from the internal tissues toward the periphery of the body.

The heat flow from the surface of the body to the medium surrounding it is governed by physical factors. It is a function of the skin to adjust the variable physiologic to the fixed physical factors, so as to permit the maintenance of a constant body temperature within a wide range of internal and environmental changes, (Lane, 1924).

The ability of the skin to lose heat may vary between ten and forty calories per square meter per degree C. It depends chiefly on the state of the cutaneous circulation, the thickness of epidermis, corium, and the subcutaneous fat deposit, and the presence of folds. While variations in thickness of the epidermis and corium are of minor importance only, the presence of abundant fat deposits in the subcutis may form a serious obstacle to proper temperature regulation. The heat conduction of fat is very low, and it is for this reason that obese persons suffer more from the summer weather. Skin folds increase the body surface and thus permit a greater loss of heat by radiation. The most important factor in the regulation of thermal conductance, however, is the cutaneous circulation, (Carrier, 1922). In a cold environment, vasoconstriction restricts the cutaneous blood flow. As a result, less blood is brought to the skin and the body heat is conserved.

In addition, the speed of the circulation of blood in the skin is diminished, thereby cooling it so that the thermal difference between the skin and the outside temperature is effectively reduced. In a warm environment, the reaction is reversed.

The mechanism of these vascular reactions is a very complicated one. There are three different types of regulation; local, central, and reflex. Local vasodilitation and vasoconstriction is probably governed by such factors as the rate of oxygen consumption of the tissues, the presence of metabolites, and the liberation of "H" substance. The central regulation is effected via the hypothalamic temperature center in response to temperature changes of the blood. An additional reflex control also seems to exist, as vasodilitation may be elicited by such a small rise in skin temperature as to exclude any significant changes in metabolism or blood temperature, (Muller, 1925).

Under ordinary conditions radiation is responsible for about 60% of heat loss, convection and evaporation of moisture for the rest. It would be fallacious to postulate any standard values, because the rate and type of heat loss depend closely on such inconstant external factors as the temperature of the air, atmospheric humidity, wind velocity, or the body surface exposed, (Hall, 1921).

It was shown that evaporation becomes important only when the external temperature rises considerably above normal. Evaporation of one gram of water causes a heat loss of 0.54 calories. This enables us to endure temperatures of 100 degrees F and even higher, provided the air is dry, for heat can be given off in spite of the reversed thermal gradient. Where evaporation assumes primary importance in temperature regulation, as for instance in tropical countries, up to 15 liters of fluid may be drunk and as much as 12 liters sweat secreted daily. When air currents are absent and the atmosphere is highly saturated with moisture, evaporation is impeded and radiation and conduction assume greater importance, especially since moist air is a better conductor of heat than dry air, (Lane, 1924).

Respiration

The respiratory activity of the skin depends on its permeability to gases and vapors, in which function it is accessory to the lungs. The manner in which this is accomplished is through a diffusion between the circulating blood in the capillaries and the atmosphere. Ernstine (1932) is of the opinion, however, that venous congestion does not alter the rate of cutaneous respiration.

There are four substances involved in cutaneous respiration: Water, oxygen, carbon dioxide, and nitrogen. Water is expelled through the skin in the sweat, and does not represent more than 1/10 of all the water expelled from the body, (Sonderstrom and Du Bois, 1917).

The factors which govern the state of hydration of tissues and the metabolism of water have not been completely determined. It is known that a change in the water content of the organism is usually accompanied by a change in the inorganic salt balance. Sodium chloride produces a negative potassium balance, potassium chloride causes an increase in the excretion of sodium and potassium resulting in a negative balance for these two elements. Ammonium chloride ingestion produces a negative balance in sodium and potassium with increased ammonia formation and titratable acidity and a loss in body water. Sodium bicarbonate causes a slight water retention, a negative sodium balance, a positive potassium balance, a slight decrease in chloride excretion, and a marked decrease in ammonia formation, (Wiley, 1933). There is only a trace of nitrogen expelled through the skin.

Carbon dioxide is eliminated through the skin and oxygen is absorbed. The rate of carbon dioxide elimination per hour per square meter of skin surface at 27 degrees C varies in different individuals from as little as 40cc to 146cc with an average of about 80cc. The average amount of exygen absorbed through the skin is 1.9% of that absorbed through the lungs, and the carbon dioxide expired through the skin is 2.7% of that excreted through the lungs, (Ernstine and Volk, 1932).

There are a number of factors which influence cutaneous respiration. The respiratory quotient at 27 degrees C averages 1.4, varying between 1.1 and 2.0. With each degree rise in temperature of the air in contact with the skin, an average increase of 8cc per hour, per square meter of skin surface occurs in both carbon dioxide elimination and oxygen absorption. The accelerated rate of gas exchange through the skin at higher temperature probably is due principally to an increased rate of cutaneous metabolism, (Ernatine and Volk, 1932). This exchange of gases is indirectly proportional to atmospheric humidity,(Shaw, 1931).

When the skin is surrounded by air containing approximately 8.5% carbon dioxide, a condition of equilibrium is established. When the concentration is decreased, carbon dioxide passes from the skin into the air, and when the concentration is increased, the reverse occurs. Oxygen is absorbed by the skin even when the air contains less than 0.5%. There is no elimination of oxygen through the skin, (Shaw, 1931). The avidity of the skin for oxygen of the air, at tensions as low as 3 or 4 mm of mercury affords evidence that the skin, under normal conditions must utilize the oxygen available from this source in addition to that supplied by the blood. The rate of oxygen absorption decreases progressively as the carbon dioxide tension of the air increases. Neither the rate of carbon dioxide excretion nor of oxygen absorption will constitute an absolute measure of the rate of metabolism in the skin, but is undoubtedly a fairly reliable index of the relative rates of metabolism,(Shaw, 1931).

Cutaneous respiration is also influenced by age, being decreased in patients over forty. This is to be explained on the basis of a generally decreased metabolic rate, (Ernstine, 1932).

It has also been shown that vitamins influence cutaneous respiration. Vitamin D has an effect on the vitality of theskin. Whether this effect is a direct one, the vitamin acting on the calcium phosphate metabolism of the skin, or an indirect one through change in blood calcium and phosphorous, or through the thyroid can not be said, (Presnell, 1937). Vitamins B and C are also thought to have an affect, the exact nature being unknown, (Amersbach, 1941). Lastly, cutaneous respiration is influenced by the presence of pathology in the body. In wide spread cutaneous lesions there is an increase in the metabolic rate of the skin with a resulting increase in the respiratory rate, (Ernstine and Volk, 1932). Toxic agents, antiseptics, anesthetics, and cosmetics decrease skin respiration, (Amersbach, 1941) while febrile conditions increase it, (Levine and Wilson, 1927).

Fat Metabolism

The skin has its own specific metabolism of fat, various minerals, and carbohydrates, (Rudy, 1934). This topic has only recently occupied the attention of well trained investigators. The findings have been of great significance, and much work is yet to be done before the complete picture can be presented.

The metabolism of fats and carbohydrates was one of the first topics to be investigated, (Rudy, 1934) and Dr. Kooyman was one of the first men to produce significant results, (1932). He found that the normal loss of lipids is about 5% of the intake, and occurs chiefly in feces, and to a smaller extent in the sebaceous secretions of the skin. The lipid secretions of the skin consist of sterols, sterol esters, neutral fats, and a small amount of phospholipids. Neutral fats are found in the sebum or oily secretion of the sebaceous glands while the sterols and sterol esters are derived both from these glands and from the disintegration of cells in the horny layer. The sebaceous secretions are important for maintaining a normal condition of the skin. Human skin and hair normally contain about 7 and 4.5% respectively of total lipids. Skin lipids are increased by vasodilitation, inflammatory processes, eczyema, psoriasis, acne and by high fat diets. They also exhibit poorly defined relations to the sex hormones. Increased secretion by the sebaceous glands is termed seborrhea. The external fatty layer of the skin is somewhat hydrous, due to the sterol complex lipid fraction. Rancidity and the secretion of lactic acid are responsible for its acid reaction, (Engman and Kooyman, 1934). Fat soluble drugs are absorbed by the skin. They are usually applied as ointments in lanolin or oils. Penetration of water-soluble substances seems to be prevented by the stratum lucidum. It has been reported that rather large quantities of olive oil (100 grams or more) can be absorbed through the human skin during vigorous massage; the absorption occurs mainly through the follicles of the sebaceous glands. The action ultraviolet rays on the skin produces inflammation, pigmentation, and splitting phospholipids the important chemical changes in the sterols , such as, the synthesis of Vitamin D from ergosterol, (Cornbleet and Popper, 1942).

The nature of the fatty substances in a tissue reflects in a general way its physiological activity. In inactive tissue, the lipids are neutral fats, i. e. simple esters of fatty acids with glycerin. In active tissues, such as, liver, kidney, lung, muscle, there are small amounts of fat, and large amounts of phospholipids and unsaponifiable lipids. The process of keratinization in the epidermis is an excellent example of cells undergoing a change in activity. The active cells in the stratum germinativum are continually multiplying, and contain many mitochondria.Cells become displaced outward, and as keratinization occurs, the mitochondria and all the cell organs apparently disappear, (Kooyman, 1932). The most striking change in the lipids of the epidermal cells during keratinization occurs in the phospholipid fraction. The phospholipid content decreases in amount. There is also a decrease in cholesterol in the cells. But, since the cholesterol seems to buffer the action of the phospholipid, the ratio of the phospholipid and cholesterol becomes important. The ratio of phospholipid to cholesterol is approximately ten times as great as in the cornified layers in the basal layers. The third change occurs in the combination of cholesterol with fatty acids to form cholesterol esters. Highly unsaturated fatty acids, characterestic of active tissues and of the stratum germinativum are destroyed or oxidized during the evolution of the cells (Kooyman, 1932) on the surface of the skin.

The fatty s bstances on the surface of the skin perform several functions. They form a water-repelling, protective film, keep skin supple and soft, and contain the precursors of vitamin D and other substances which are activated by irradiation at the surface of the skin. These lipids may also play a role in contact dermatitis. There are two types of skin lipids - the unsaponfiable and the saponfiables. The unsaponfiable material constitutes 27-36% of the total lipids and includes sterols and unknown fractures. The function of the high sterol and high sterol ester content of lipids is not known. It may seem as a methodof getting rid of waste products of metabolism, preserve the body surface in a condition required for normal physical, chemical and immunological actions, or may play an important role in the general metabolism of the body. The saponifiable substances include free fatty acids, the high content thereof being the result of lipolytic action of enzymes and bacteria of the skin, and the splitting of the higher unsaturated fatty acids by oxidation. Other saponifiable substances are oleic acid, arachidonic acid, and palmitic acid, (Engman and Kooyman, 1934).

Fat metabolism is related to vitamins. Vitamin A flourescence is found only in adjacent fat tissues, and not in the epidermis itself. Other lipids of the skin - the oil glands and surface fat are free of vitamin A. Feeding of large amounts of vitamin A does not produce a storage of vitamin A in the skin, though the skin is one of the first sites to react to a vitamin A deficiency, Cornbleet and Popper, 1942).

In vitamin G (B_2) deficienty, the total fat content is markedly decreased, while the phospholipid content shows only a slight increase. There is also a decrease in the oxidative ability of the skin itself, and is manifested chemically in loss of hair and dermatitis, (Adams, 1936).

Carbohydrate Metabolism

There are relatively wide variations in the sugar content of the skin, depending on, (1) the methods of taking samples, (2) the areas from which the samples are taken, (3) the method of preparing the skin for analysis, and finally, (4) the chemical methods used in determining the dextrose and glycogen levels, (Cornbleet, 1940). The average figure now reported is 58 mgn per 100 grams of skin. The level rarely rises higher than 65.3 with 68 and above being considered as pathological, (Urbach, 1945). The bound sugars, those reducing substances which remain in the protein precipitate, perhaps glycoproteins, are of uncertain importance. It is the dextrose and glycogen which are the most important indicators of normal or disturbed carbohydrate metabolism, (Cornbleet, 1940). It is noted that the skin serves as a temporary storehouse for large amounts of dextrose. Drs. Folin, Trimble, and Newman (1929) showed that during fasting conditions, the dextrose level is almost zero. When the blood sugar level rises, there is a rise in skin dextrose by 50% of the blood level. The skin thus becoming an important "outlet" for blood sugar. Dr. Cornbleet, however, is of the opinion that, while dextrose in the skin represents a diffusion product from the blood, the skin is not a site for dextrose storage.

He points out that the cutaneous sugar rises and falls with the blood dextrose after a very short latent period. After the transfer of quantities of dextrose into the skin from the blood, an increase occurs in the cutaneous glycogen, an appreciable time elapsing during this conversion of dextrose to glycogen. "The skin can hold the flood tides of dextrose from receding rapidly, only if it converts it to starch. When the recession occurs, the glycogen slowly ebbs too, to a certain degree. The levels of glycogen and dextrose do not necessarily follow each other", (Cornbleet, 1940). Under the action of insulin, the dextrose of the blood and that of the skin decreases, while the glycogen in the skin shows an increase. It is known that one of the actions of insulin is to aid in the synthesis of glycogen, (Cornbleet, 1940)

There is, in man, a fairly constant ratio between the dextrose content of the skin and of the blood, but following the ingestion of large amounts of dextrose, this ratio may be disturbed, (Palmer, 1917). Cutaneous sugar levels reach a peak in about one hour, and return to "normal" within three hours, while blood levels are one half and two hours respectively. The sugar content of the skin may be regarded as a simple diffusion process, (Pillsbury, 1940). The relationship between blood sugar levels and skin dextrose levels may beexpressed in terms of four curves, (Urbach and Sicher, 1945). First, in normal individuals in which the resting value of skin dextrose in 40-50% of the blood sugar, the maximum level of the skin dextrose is reached in one hour following the ingestion of 100 grams of dextrose. The rise is not abrupt, nor is it as high as the blood sugar. Whereas, the blood reaches fasting levels in two hours, the sk in commonly requires three hours. Secondly, the blood and skin may reach very high values, the maximum being delayed for 2-3 hours, and requires five hours to regain the fasting level. This curve is denominated the "diabetic blood and skin dextrose tolerance curve", and has been noted in cases of pruritus, eczema, furunculosis, and gangrene. The third curve is called the "sympathetic endocrine curve" and is characterized by the blood sugar reaching a high level (320) within an hour, and rapidly falling. There is no abnormal increase in the height of the skin sugar curve. This has been noted in cases of ulcer curis, and chronic ulcerative pyodemma. The fourth curve is characterized by the skin dextrose level exceeding that of the blood. The blood sugar increase is normal, while in the skin, the sugar level is greatest. The skin level rises rapidly and returns slowly to fasting levels. This curve is considered as evidence of a latent diabetes, (Urbach, 1945). The important thing to consider is not the amount of cutaneous sugar per se, but the ratio of skin and blood sugars which is normally 61%, ratio of 70 or more being regarded as "independent cutaneous glycohistechia", (Urbach, 1945).

There are three substances which play an important role in cutaneous carbohydrate metabolism. The first of these is insulin, the second is enzymes, and the third is epinephrine. Insulin, normally present in tissues, appears to play a significant role in carbohydrate metabolism. Up to an optonal amount, insulin increases the metabolism of sugar in the skin, but to a much less extent than in muscle. Therefore, cutaneous sugar is reduced and at the same time glycogen is deposited in the skin at an accelerated rate when there is an excess of insulin. This tends to retain carbohydrate in the skin as a reserve supply, (Cornbleet, 1940). The skin contains enzymes which make possible the transformation of dextrose with the production of lactic acid, (Cornbleet, 1940). The enzymes present are glycolytic and diastasic enzymes, diastase being the chief one, (Pillsbury, 1931). Epinephrine is a normally circulating hormone and has an influence on carbohydrate metabolism. After the administration of the drug systemically, sugar is mobilized, derived in part from cutaneous glycogen. Hisamine produces delitation of the capillaries which causes an increase in the permeability of the capillary walls resulting in a more rapid diffusion of sugar into the skin. Epinephrine has exactly the opposite effect, (Cornbleet, 1940).

There are other local factors which are important. Local heat increases circulation and speeds up metabolism while local cold has the reverse effect. Ultraviolet rays produce a decrease in blood sugar, if mild, an increase if erythema is produced, and cutaneous glycogen levels follow the blood levels. The beneficial action of roentgen rays in clearing up some cutaneous lesions may be due, in part, to changes in the metabolism of cutaneous cells. Irradiation alters the oxidation - reduction reactions with resulting changes in carbohydrate metabolism. Dextrose is increased locally, glycogen remains unchanged. The effect of the contact of ice with the skin is first to reduce the dextrose content of that part of the skin. Later, when the skin becomes congested, the dextrose content is increased. At the same time, the glycogen value r emains stationary, (Cornbleet, 1940).

The exact purpose and action of cutaneous glycogen is not certain. Apparently it does not exist in the skin merely as storage material to furnish dextrose as does the glycogen in the liver. If the liver is removed, the blood sugar drops rapidly. Muscle glycogen has an action of its own apart from that of furnishing dextrose and it appears that the metabolism of glycogen in the skin follows somewhat the form it takes in the muscle and not in the liver. Glycogen may exist as a protecting substance, being necessary for the protection and detoxifying process in the liver. These processes may be concerned with the mechanism of immunity, though the exact function is not certain, (Cornbleet, 1932).

Lactic acid is an important product of carbohydrate metabolism, and occurs in the skin. The cutaneous lactic acid level of starved animals is low, while that of well fed animals is normal. There is evidence that the skin transforms dextrose into lactic acid, though it plays a very small role in the formation of glycogen. The cutaneous glycogen is distributed as follows:

1. In epidermis - 226-344 mgm %.
2. In corium - 71-157 mgm %.

Moderate to marked amounts of glycogen are the rule in non-diabetic skins, and the skins of diabetic patients show lower levels, a most interesting observation, (Pillsbury, 1931).

It was fourteen years later, that Dr. Urbach published his conclusions relative to diabetes and skin sugar levels. He observed that in resistant dermolotogical cases, improvement often resulted from the institution of a diabetic diet. This was noted in cases of dermatitis, furunculosis and pruritus, expecially in the elderly and obese. He also observed that diets rich in carbohydrates induced a return of symptoms. Dr. Urbach introduces the term "Independent Cutaneous Glycohistechia" to suggest a rise in skin sugar without hyperglycemia, (Urbach, 1945). By careful clinical studies, Dr. Urbach demonstrated that a patient with a normal fasting blood sugar level could, at the same time, show more or less of an elevation of the fasting skin level, i. e., greater than 80 mgm per 100 grams of skin. In these patients, often diabetic management served both to clear up the dermatosis and to lower the skin sugar level.

The term "skin diabetes" is suggested as a designation for the syndrome of therapy resistant skin disease, high fasting skin sugar level together with a normal blood sugar curve, and a pronounced improvement of the dermatosis, as well as, a fall in high skin sugar level on a low carbohydrate diet, sometimes combined with insulin.

Dr. Urbach presents three points of evidence to support the contention that there is a connection between the clinical syndrome and a disturbance in the carbohydrate metabolism, as in diabetes: (1) The high fasting skin sugar levels, which attain and even exceed

80 mg. per hundred grams. (2) The pathologic and characteristically diabetic course of the skin sugar curve following oral sugar forcing. (3) The return to normal of the fasting skin sugar level, as well as, of the skin sugar tolerance curve after a low carbohydrate diet, notably in combination with insulin.

Genuine pancreatic diabetes would seem to be excluded by the virtually normal behavior of the blood sugar tolerance curve and by the fact that it has not been possible as yet to demonstrate that such a case ever progresses to frank diabetes. Aside from the question"... as to whether or not cases presenting independent cutaneous glycohistechia are actually to be regarded as cases of"skin diabetes", it may be safely said, on the basis of clinical experience, that a diabetic diet should unhesitantly be tried in cases of therapy resistant skin diseases as furunculosis, eczema or pruritus, even when the blood sugar tolerance test is normal", (Urbach, 1945).

Mineral Metabolism

The skin normally contains a variety of minerals, including potassium (247 mgm. per 100 grams of skin), calcium (42.8) and sodium (32.50), (Cornbleet and Ingrahams, 1942). With injury to tissue cells, there is a passing of intracellular potassium into the blood. It has been shown that histamine causes injury to cells resulting in a loss of intracellular potassium into the blood. In wheals, potassium, sodium, and calcium,values are lower than in the normal skin, (Cornbleet and Ingraham, 1942). It was also demonstrated by Drs. Cornbleet and Ingraham that calcium and potassium show other interesting reactions. After the administration of potassium,the calcium content of the blood is definitely and uniformily raised, while the skin calcium level is not changed. An increased calcium reduces the permeability of the blood vessels, and constitutes one method by which the skin attempts to combat the formation of wheals. In a histamine wheal, the amount of potassium decreases, probably because the cells give up some of their potassium when irritated or injured. These authors also conclude that an increased irritability is associated with an increased potassium and decreased calcium, and that an increased capacity for sensitization is coupled with lowered potassium concentrations.

The skin also contains traces of magnesium, the exact importance of which is not clear, (Eisels and Eichilberger, 1945).

Silicon is present in small amounts, and is mobilized from the deeper part of the dermis to the outer third of the skin, and probably from the whole body of the skin in pemphigus. It is suggested that the role of silicon is concerned in healing and fibrosis, although its crystals may be responsible for the formation of the lipo-protein "foam" in the outer portion of the dermis, (MacCardle and Baumberger, 1943).

The ash content of normal skin fluctuates between hypermineralization and hypomineralization in children until about age ten when a definite change toward hypermineralization begins and proceeds slowly and unbroken until old age. The epidermal cells of normal skin contain much white ash of calcium and magnesium. Silicon is present in the nucleoli of all cells. The primary mineral change in old age appears to be a shift of calcium and magnesium from the deeper part of the epidermis to the corium and dermis and a decrease in the amounts of silicon. In neuro-dermatitis, there is a mineral loss with a decrease in silicon, calcium, and magnesium. Most of the iron in the normal skin is retained in a biologically active organic state, (MacCardle and Engman, 1943).

Mineral metabolism is also affected by sweating. When the human body is not sweating, no calcium or phosphorous is lost while sodium, potassium, chloride, and sulfate sulfur are lost. The cutaneous loss of sodium and chloride does not vary w th the intake or urinary output of sodium chloride, (Freyberg and Grant, 1937).

Sulfur is a very important mineral in the skin and exists essentially in organic combination, a large portion being in the form of cystine and cysteine, Rimington, 1934). Some exists in glutathione and methionine, Sulfur metabolism plays a defensive role a nd cystine and glutathione are important detoxifying substances. In his observations, Klauder (1936) found that half of the patients dying of chronic infections, and in the majority of those dying of tuberculosis, there was a low or low-normal sulfur content of the skin. Cystine is the only aliphatic amino-acid of the protein complex which has any marked absorption for solar ultraviolet rays. From this, it appears that the protective action of keratin- containing tissue against ultraviolet rays is due to the sulfur containing cystine complexes, (Ward, 1923).

It is interesting to note that the sulfur content of the skin decreases with age. The normal percent of sulfur in infants is 0.40%-0-50% and decreases the first few years of life to about 0.35%. At adolescence it is about 0.30% and in adults 0.25% to 0.30%. This is in accord with the knowledge that the sulfhydryl containing amino acid cystine in one of that limited groups of amino acids which is indespensable for normal growth and development, (Klauder, 1936). It has also been demonstrated that the action of arsenic on protoplasm is essentially due to an action on certain organic sulfur compounds containing sulfur in the mercaptan (sulfhydryl) form (Voegtlin, Dyer and Leonard, 1925).

In disease processes, the metabolism of sulfur is upset. In psoriasis the non- protein sulfur is somewhat increased, (Levine, 1932). It may be that the therapeusis of psoriasis should be directed toward decreaseing the high percent of sulfur. Sulfur containing compounds, especially glutathione are essential physiologic tissue constituents concerned in biologic oxidation - reduction phenomena. There is evidence that the pathogenesis of psoriasis concerns the oxidation- reduction mechanisms of the epithelial cells, (Klauder, 1936).

Benign and malignant melanomas are rich in sulfur. Experimental results do not prove, as yet, whether malignant tissue contains more glutathione than surrounding normal tissue. The skin serves as a depot for sulfur on which demands are made as part of the defensive mechanism operative in infections and intoxications. Sulfur in organic combination, especially compounds containing the sulfhydryl radical or divalent fulfur, act as detoxifying agents, (Klauder, 1936). Harmmett (1929) reports a gross acceleration of wound healing by the simple external application, not only of cystine but also of thiodextrose and thio-cresol.

Conclusions

The skin is one of the organs of the body, and has a number of characteristic functions which depend upon its anatomical structure and chemical - physical constitution. It has been shown that the physiology of the skin depends upon blood and lymph circulation, along with nervous coordination. The enzymes, fatty acids, lipids, sterols, minerals, water, and salts represent some of the chemical constituents which govern the skin's function, while acidity, electrical resistance, osmotic pressure, temperature, and irradiation represent some of the physical constituents which compliment the chemical.

One group of physiological functions of the skin has to do with the outside of the body. The skin serves as an organ of protection and reception in addition to forming a first line of defense by virtue of its self-sterilizing properties which are dependent upon the acidity of the sweat, the presence of long chain fatty acids and the esters thereof, and the proper cutaneous metabolism of carbohydrates especially.

The second group of functions pertains to the skin *per se* and the interior of the body. The chief secretory product is sweat; the chief excretory product is sebum. The nature, composition, and function of both has been indicated. The processes of sensitization, immunity, and pigmentation await further investigation before definite conclusions can be reached, but the accepted theories relative to each have been presented. The skin as an organ of storage for salts, water, minerals, sugars, lipids, et al, has been described.

The skin also has functions concerning both the body exterior and interior. Heat regulation and cutaneous respiration have been briefly presented, and more space given to cutaneous metabolism, a field of recent investigation, and one in which there is much yet to be done. The skin has its own metabolic processes quite apart from, though coordinated with general body metabolism. Cutaneous metabolism, as it is understood at present has to do with fats, carbohydrates, and minerals, and is influenced by the general body conditions, vitamins, and a host of other factors.

Throughout the discussion, it has been repeatedly borne out that the skin, being one of the body organs, is a mirror of body pathology as well as having a pathology peculiar to itself. The classic example of this latter condition is skin diabetes recently announced by Dr. Urbach.

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