parent substance, which spreads over the entire papillary layer in an extremely thin stratum. The presence of double contours nowhere, however, indicates the existence of a membrane. This intermediate substance, which also penetrates into the interior of the papillary layer, and is probably identical with the so-called cement-substance, can be removed by trypsin, and then, with the outline of the furrows, the clear external border of the papillæ also disappears, and the connective-tissue fibrillæ are laid bare, some of them spreading out like a brush, others having the form of loops.

Papillary Vessels.—The majority of the papillæ are the carriers of capillary vascular loops running vertically through their centres, the main office of which is to provide for the nutrition of the epidermis, the respiratory function of the skin, and the production of watery sweat. The capillary loop consists of an arterial and a venous branch, which unite a little below the apex of the papilla, and run a straight or a curved course according to the amount of their contents and the retraction of the papillæ. The waviness may attain such a degree that the loop fills almost the whole of the papilla. This allows us to infer a great variability in the length and calibre of the capillary loop in vivo. In some papillæ, a number of arterial branches empty into the venous capillary.

A small proportion of the papillæ contain a tactile corpuscle instead of a capillary loop; in rare instances, a small capillary loop passes up a short distance into the papilla beside the corpuscle.

In close contact with the papillary layer lies the epidermis,[1] although no genetic relation exists between them them. All the attempts which have been made, even quite recently, to demonstrate the origin of at least a part of the epithelial formation from the connective tissue, must be regarded as failures. The epidermis has its own matrix, the ectoderm, and after losses of its substance, is regenerated only in case portions of the ectoderm have been preserved, in the shape of epidermis, hair-papillæ, or ducts of glands.

Development.—Consisting originally of a single layer of polygonal cells, it presents in the second month a second row of smaller substitutive cells, which make their appearance between the first layer and the corium. While the outer layer, in consequence of the flattening of its cells, gradually comes to resemble the subsequent horny layer, the lower one gradually becomes thickened, from the third to the fifth months, into one containing from two to four rows of cells, which may already be recognized as the prickle-layer on account of the presence of fine connecting threads between the cells. The increased vascularity of the corium in the second half of fœtal life entails a marked increase in thickness of the prickle-layer. The horny layer, however, remains thin, and at the seventh month has only two rows of cells, the outermost non-nucleated scales mixed with fat, being transformed into the vernix caseosa, or gradually thrown off and mixing with the liquor amnii. As early as the eighth month granular cells make their appearance between the prickle and the horny cells, and a more complete cornification occurs, which puts an end to further desquamation of the epidermis. The thickness of the epidermis (0.15 to 0.25 mm.) is at birth considerable, in comparison with that of the corium (0.7 to 0.9 mm.), when we contrast with it the relation of the two layers in the adult. This disproportion ceases between childhood and the period of puberty, as the epidermis increases but little in thickness. If we also bear in mind

[1] It is to be hoped that the erroneous designation of the horny layer as "the epidermis" may soon finally disappear from scientific works.

that from the fifth to the eighth month all the hairs and coil-glands are developed from outgrowths of the prickle-layer, we gain some notion of the luxuriant growth of this germinal layer at the period mentioned. This quantitative increase is due almost entirely to cell-division, the individual epidermic cell in the adult being but little larger than in the fœtus. In this way proof is also furnished of the astounding productivity of the epidermis, the general surface being one hundred and forty-five times as large in the adult as in the fœtus (Harting). During the fœtal period, the cornification is not of the same hardness in all parts of the body. The horny layer is most unyielding on the dorsal aspect of the terminal phalanx of the fingers and toes, on which the original epidermis, condensed into a membrane, remains as late as the eighth month. This fact has a peculiar significance for the development of the nail. Beginning with the sixth month, the outer layers of the epidermis acquire such a firm coherence that, from this time on, the increased difficulty of its growth in thickness towards the surface no longer suffices, and the proliferating epithelium is driven downwards into the corium at some points. We have already seen how, during this process, certain more resisting portions of the latter are entirely surrounded by the growing epithelium. It now only remains to take a nearer view of the forms of epithelium thus produced. It is not enough to describe the portions of epidermis which penetrate between and give form to the papillæ, as "cone-shaped." It is true that, on transverse sections of the skin, the epithelial processes seem, as a rule, to be conical in shape, but they are also often club, nail, and hump shaped.

Form of the Epidermis as a Whole.—In horizontal sections of the skin, however, they completely fill the spaces between the circular cross-sections of the papillæ. Their real configuration is, therefore, a more complicated one; it is the negative of that of the papillæ, and, therefore, a plate with numerous conical depressions upon its under surface.[1] If a vertical section cuts through a row of such depressions, the cut surface presents a corresponding series of conical epithelial outgrowths, but if it falls exactly between these depression, the epithelium, of course, presents a straight outline towards the corium. In places where the papillæ stand in regular rows, it is, therefore, possible to make at will sections with either a wavy or a straight border toward the epidermis. It is evident that great caution is necessary in judging the border-line between the epithelium and the corium in pathological cases; it can with safety be determined only on a continuous series of perpendicular sections after comparison, if possible, with horizontal sections. Just as little can one obtain a notion of the bulk and superficial extent of the epidermis by single measurements of the height of the epithelium between and over the papillæ. Here also the relative extent of the papillary layer and the epidermis must first be determined on horizontal sections, and the cross-section of the papillary layer thus ascertained must be multiplied by its thickness, and subtracted from the cubic contents of the entire epidermis.

It is, however, a different matter with the epithelial processes which are not formed by the growth into the corium of the epidermis in toto, but by further sprouting of single, more highly favored portions of the epidermis, after the papillary layer has already been formed. These assume, without exception, while penetrating into the meshes of the corium, the shape of cones, like the epithelial sprouts from which the sweat-glands and hairs are formed. The process of growth and new formation of papillæ (on the hairs), which continues through the whole of life, is the physiological prototype of the irregular growth of the epidermis in pathological cases (infiltration of the corium, tumors). In such cases, according to the direction in which the section is made, there are

[1] Whence the ancient, inappropriate name rete (Malpighi).

found dendritic and branching conical figures. The surrounding of portions of the corium by the epithelium, however, never goes as far as the complete cutting-off of mature fibrillary tissue, whereas masses loosely embedded in the corium (collections of round cells, blood-clots, heaps of pigment), which do not contribute to the nutrition of the skin, may indeed be completely surrounded, if growing epithelium comes in contact with them.

It follows from all this that the name epithelial cone, which is frequently given to the interpapillary portion of the epidermis also, is inappropriate. But, as a short designation is necessary for those portions of the epidermis which lie over and those which lie between the papillæ, we shall call them the "interpapillary prickle-layer" and the "superpapillary prickle-layer."

Layers of the Epidermis.—We divide the epidermis into three layers: 1, the prickle-layer; 2, the granular layer; and 3, the horny layer. The innermost, which is seated directly upon the papillary layer, is the prickle-layer, which consists of so-called pavement epithelium, of an approximatively cubical shape, piled up in a varying number of rows of cells. Close to the border of the corium the shape of these cells is usually cylindrical, for which reason they were formerly distinguished from the rest of the prickle-layer as "cylindrical cells."

Prickle-layer.—A little higher up in the epidermis, rounded and cubical cells make their appearance in the interpapillary spaces, and horizontally flattened cells in the superpapillary region. All these cells have as a common characteristic a thick *armor of prickles,* composed of fine protoplasmic processes.

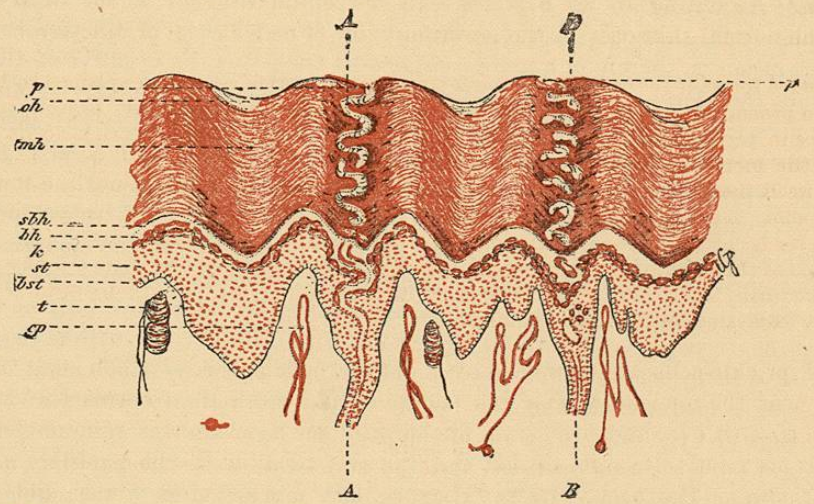

FIG. 3.—Epidermis and papillary layer.—Picrocarmin staining.—Decolorization of the picric acid by alcohol and water. *P*, sweat-pore; *o h*, superficial horny layer; *m b*, middle horny layer; *s b h*, superbasal horny layer; *b h*, basal horny layer; *k*, granular layer; *s t*, prickle layer; *b s t*, basal prickle layer (cylindrical cellular layer); *t*, tactile corpuscle; *c p*, capillary loop; *A-A*, *B-B*, excretory ducts of sweat-glands.

The differences in the shapes of these prickle-cells are due as a rule to demonstrable mechanical influences. Thus the cylindrical form of the basal cells is the result of their greater productivity. We here find a constant new-formation of the epithelium by indirect division of nuclei and cells. As the younger basal prickle-cells must of necessity push themselves in between the older ones, all the cells in this part are flattened and narrowed in a direction parallel to the corium, and elongated in one vertical to it. Such is the appearance presented by the basal prickle-layer when the new formation is moderate, particularly when active proliferation is followed by a long period of rest, as is generally the case in the adult. When the growth of the epithelium is very active, on the other

hand, a layer of cylindrical cells is not again formed, for the reason that many of these cells constantly lose their upper halves during cell-division. In this case, the lowermost layer of prickle-cells is filled with several rows of young rounded cells.

We may obtain some notion of the situation and extent of the productive portions of the prickle-layer in the normal and pathological skin by utilizing the property of the mother and daughter cells during their division, of becoming much more vividly stained by good coloring agents than the older prickle-cells in the same sections.[1]

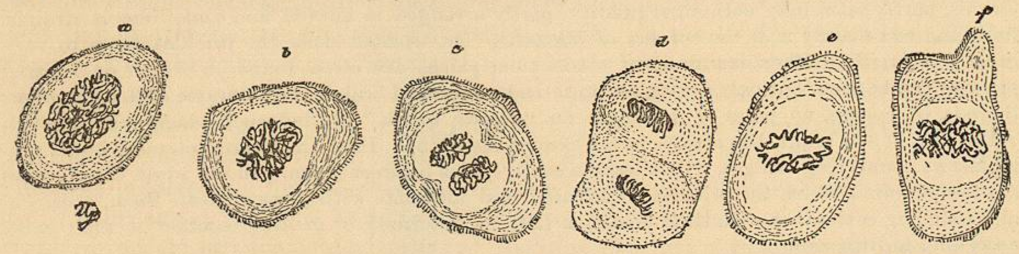

FIG. 4.—Indirect division of nuclei and cells.—Prickle-cells from a condyloma. *a*, coil-like nucleus, *b*, the same with loops partly torn through; *c*, coil-like daughter-nuclei; *d*, star-shaped daughter-nuclei; *e*, star-shaped mother-nuclei; *f*, as *e*, probably an equatorial plate (Flemming).

In order to prove the proliferation of epithelium, it is also essential in the present state of science to demonstrate the occurrence of division of nuclei and cells at the point in question. According to my previous experience, appearances which show this are found in the normal skin only in the lowermost row of cells in the prickle-layer.

The rounded forms of the cells in the middle stratum of the prickle-layer is explained by the tolerably uniform pressure from all sides of the neighboring cells, while two factors exercise a controlling influence in producing the horizontal broadening of the superpapillary prickle-cells. In the first place, the increase in extent of the surface of the body in each successively higher layer of cells makes itself the more felt directly over the papillæ the less it is counteracted by cell proliferation at this point; in the second place, at this level the proximity of the firm, horizontally spread out horny layer is calculated to make these cells assume the shape of thick plates.

The shape of the prickle-cells is, however, not exactly defined by calling them cylinders, cubes, and plates, because all the cells, particularly those in the lower layers, have their surfaces facetted and partially excavated, or rendered angular.

All the prickle-cells are composed of a hollow globular body, which ends abruptly internally, near the nucleus, with a sharp contour, and externally towards the neighboring cells, is covered over and over with fine protoplasmic processes. The nuclei of the prickle-cells are relatively large, so that their thready structure becomes visible with low magnifying powers (Hartnack, VIII.). They contain one or more nuclei, and are not bounded externally towards the body of the cell by a membrane, and are therefore not really vesicular bodies. The nucleus lies in close contact with the body of the cell; the clear space visible between them, in some methods of preparation, is artificially produced. The shape of the nuclei in the upper layers, which are less exposed to the pressure of the neighboring cells, is a regular oval, in the lower layers round or rod-like, according to the shape of the cell, and the long axis of the nucleus in the different layers of the prickle-layer always coincides with that of the cell, except during division.

[1] In order to furnish a good selection to the staining agent, it is necessary (as is advisable in all cases) to afterwards decolorize the over-stained sections; *e. g.*, hæmatoxylin should be removed by momentarily dipping the section into glacial acetic acid, carmine in aqua ammonia, etc.

Max Schultze was the real discoverer of the prickly coat of the isolated cells; he believed that they fitted closely into each other, like the teeth of two watch-wheels. Bizzozero, on the other hand, believed that the prickles of two adjacent cells melted together at their points, and Lott took a middle position, maintaining that the points of the opposing prickles are in contact by their sides. Ranvier finally again inclines to the view of Bizzozero. According to him, the opposing prickles melt together and form an elastic nodule, a peculiar "elastic organ," which permits a considerable lengthening of the prickles.

Seen from the surface, the prickles appear as points, in profile as completely isolated fine bristles usually with pointed extremities. They are attached to the body of the cell at tolerably regular intervals, partly seemingly without regularity, partly arranged in curved, and sometimes in straight lines, the last mainly near the corners of the cells. On isolated cells the prickles seem to vary greatly in length. When examined in connection, places are often found in which no isolated prickles can be seen, but only protoplasmic threads, stretched bridge-like from one cell to another; there is, of course, no point of junction, no "elastic organ." I find such places often enough n the skin of the adult, but always in the skin of the fœtus. Here they form tolerably broad protoplasmic connecting bridges, which leave narrow spaces between them. In the adult, other places are also found in which the prickles are isolated, and alternate with those opposite them, occasionally touching each other with their points, as Lott has described, or melting together at their ends, according to Bizzozero.

In still other cases, and especially where a wandering cell which has crept into the interspinal spaces lies close to an epithelial cell, the prickles of this side of the cell have disappeared for short distances (see Fig. 5), while the opposite cell sends out its prickles freely. Finally we see prickles of very great length, which Ranvier also describes, which unite, not the nearest points of two adjoining cells, but more remote ones, running partly entirely around one, and going over to another.

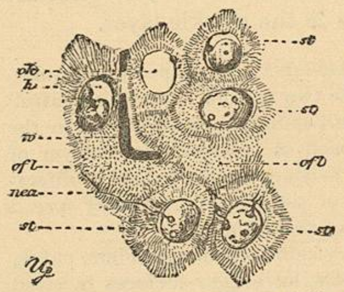

Fig. 5.—Small portion of the prickle-layer, interepithelial terminal nerve branches, and intra-epithelial terminal nerve-bulbs; wandering cells. Section treated with ether, osmic acid, hæmatoxylin, glacial acetic acid. *o f l*, prickle-cells seen from the surface; *o k*, prickle-cell without nucleus, which has fallen out; in the cavity thus formed a terminal nerve-bulb is visible; *n e a*, terminal nerve branch; *s t*, prickle-cells with two terminal nerve-bulbs; *h*, cavity near the nucleus produced by its shrinking; *w*, wandering cell, lying in a dilated interspinal space; a little higher, a fragment.

It will be seen from these different appearances that it is impossible to accept any one of the views given above as the normal standard. The most likely view is to regard the form of the simple protoplasmic connecting bridges as the original one. These bridges are, however, exposed to the influences of the lymph which flows around them, to the ingrowth of nerve-threads, to immigration of white blood-corpuscles, and to the more or less great alterations in the situation of cells which originally lay close to them; we must, therefore, in view of these facts, attribute to them the faculty of being passively, and perhaps also actively, drawn in and out. It is unnecessary to imagine the presence of "an elastic organ" in the threads, which to me seems particularly untenable and superfluous for the reason that short bridges without the intermediate nodules occur just as frequently as long ones which present such nodules in spite of their elongation.[1]

We must, therefore, regard the prickly sheathing of the cells as a system of protoplasmic processes engaged in active movements, which permit the free circulation of the nutritive current through its spaces, and effect an organic connection, very firm, but not inalterable between adjacent cells. The older the prickle-cells in the higher layers become the shorter are the prickles, and in the succeeding layer of granular cells the connection is always reduced to straight connecting bridges. The prickle-cells can only be isolated with difficulty, the prickles often breaking off rather than yield at their points of union.

[1] Attention must also be paid to the semblance of rows of nodules, in figures resembling the rounds of a ladder. Such are due to nerve-threads which pass under them, and produce optical appearances of bends.

Granular Layer.—Next to the prickle-layer comes the granular layer, which usually consists of one or two, more rarely three, and in pathological cases of even four or five rows of coarsely granular cells. *It is to this layer alone that the white race owes the color of its skin.* The granules of this layer refract the light very strongly and therefore seem dark by transmitted, and white by reflected light. Prior to the appearance of the granular cells, the entire skin of the fœtus has a glassy transparent appearance, the blood-vessels of the corium being visible through it. Only at the points at which the hairs develop does the granular layer of the inner root-sheath appear before the granular cells of the skin, and in the fœtus of six months they shine as fine white stripes through the uncolored epidermis. Near the end of fœtal life the granular layer makes its appearance at this point also. At birth, aside from the universal hyperæmia, the entire surface is white, except at two points, the borders of the lips and the nail-bed. In both places there is a normal prickle-layer surmounted by a very thick, horny mass; in both the granular layer is absent through the whole of life.

The granules, which characterize this layer, were seen long ago by Kölliker and Auffhammer Langerhans was the first to carefully describe them, without, however, recognizing their constant relation to the process of cornification. I next declared the granular cells to be necessary intermediate forms in the process of cornification on free surfaces, and demonstrated their presence in the excretory ducts of the coil-glands and in the mother-cells of the inner root-sheaths of the hair. At the same time Heynold demonstrated their presence in the vicinity of the nails, and soon afterwards v. Ebner described them very carefully in the mother-cells of the inner root-sheath, without identifying them, however, as I had already failed to do before him, with the granules of the stratum granulosum. Ranvier regarded the granules as drops of a fluid substance, which he believed to exist in a free state also, between the cells of the undermost horny layer, and to which he gave the name "eleidin."

Keratohyalin.—We owe our first exact knowledge of this very peculiar substance to Waldeyer. He showed, in opposition to the opinion of Ranvier, that it swells up under the influence of alkalies and undergoes alterations in form under pressure without melting, and could not, therefore, be fluid. The granules are rendered more distinct by the addition of glacial acetic acid and ammonia, because they are less affected by these agents than the substance of the cells. They are insoluble in water, alcohol, ether, and chloroform. The caustic alkalies and the strong mineral acids, and a pepto-glycerin extract dissolve them in the heat. They show a very great affinity for substances which stain nuclei, especially hæmatoxylin and carmin (picro-carmin)—an affinity even stronger than that of the nuclei themselves. They cannot be stained by hyperosmic acid. To judge from these reactions, they cannot be composed of fat or fatty acids; they are distinguished from nuclein by the fact that the latter is soluble in alkalies and carbonate of sodium, even at a low temperature, and from keratin by their solubility in pepsin-hydrochloric acid. No glycogen can be found in them. On the other hand, they correspond almost or absolutely in their chemical behavior to *hyalin*, a product of degenerative processes in various tissues. Waldeyer, therefore, proposes the name *keratohyalin* for the substance of the granules.

The keratohyalin does not first appear in the uppermost rows of cells, those which border on the horny layer, but in the middle strata of the prickle-layer, but only in the form of isolated granules in the neighborhood of the nuclei. We can speak of real granular cells only when, in ordinary moderate staining, cells appear the entire bodies of which are almost filled with small and large granules. The granules are visible even in unstained preparations, or in those treated with osmium, on account of their strong refracting powers, and are always rendered distinct by the addition of glacial acetic acid; but only when the sections have been stained according to the method described above does the granular layer suddenly appear as a dark-violet or red band, between the prickle and the horny layers. The granules have a rounded form; small ones are often found on top of larger ones. The large ones show lesser powers of resistance to the before-mentioned solvents (Waldeyer). Even when the cells are completely filled with granules, there always remains a slender peripheral zone free from them. This, however, is not sharply defined towards the body of the cell.

Two other kinds of changes also occur in these cells filled with granules. The first is a decided shortening of the peripheral prickles. While these are becoming shorter and at the same time broader, the cells come much closer together, and the interspinal spaces are so much lessened in size that there can no longer be a continuous current of fluid through them. In the interior of the cell the nucleus undergoes atrophic changes, seeming constricted at certain points, or assuming a mulberry or other shape, but always becoming smaller. It is still capable, however, of being well stained. The cavity in the cell-body, which was occupied by the nucleus, retains meanwhile its original size, the contracting nucleus having drawn away from its walls.

The following changes, therefore, take place simultaneously in the prickle-cells as they grow old, and that quite suddenly; the nucleus shrinks, the cell-body becomes filled with granules of different sizes, composed of keratohyalin—a substance peculiar to the process of cornification; the peripheral zone of the cell becomes differentiated, as a clear border, from the remainder of the cell-body, and the intercellular connecting bridges become much shorter and thicker; these changes characterize the granular layer, and the cells are now ready to undergo cornification.

Horny Layer.—Immediately above the uppermost granular cells the first horny cells now make their appearance as perfectly clear transparent bodies. All the strongly refracting granules have disappeared from their interior—a change which takes place very quickly. On hæmatoxylin specimens it can be seen that in the undermost horny cells very minute granules with faintly defined broad clear spaces around them are still present, and we must, therefore, believe that the granules disappear by melting into the remainder of the cell-protoplasm. At the same time the last traces of the intercellular juice-canals seem also to have disappeared at this point. It is true that these horny cells do not lie flat upon each other, and I stated in 1875 that they still present very fine teeth (rudimentary prickles) on their surfaces. But it can be very well seen, particularly on portions of the horny layer which have been digested with pepsin and trypsin, that these teeth strike upon each other, and are, therefore, on isolated cells, nothing more than broken rudimentary *connecting bridges, which remain, although reduced to a minimum, during the process of cornification.* From this it follows that the horny cells retain their connection with each other by the persistence of the connecting threads which were present from the beginning.

The method of digestion is a very important one for the study of the horny layer, for it shows that the process of cornification does not affect the whole cell, but only its outermost layer. If the digestion be sufficiently prolonged, the entire contents of the cells are destroyed, and empty shells of horny substance of the shape of a melon or a

gourd, and much elongated, are left behind. The horny layer as a whole has, therefore, the structure of a honeycomb, in which the wax-cells are replaced by horny shells. Very thin (5–10 μ thick) sections of the horny layer, therefore, show, after being digested, a large-meshed net or horny substance without contents, the strands of which are formed from two horny threads running close together, which are united by very short horny bridges. These horny threads, the cross sections of the horny membranes, are everywhere of the same thickness (about 1 μ), even throughout the entire breadth of the horny layer of the heel. Somewhat thicker cross sections, treated in the same manner, show *incised horny cells* with yellowish horny lateral walls; here, débris of nuclei can also be found, after digestion with pepsin, even in the highest part of the horny layer. It has hitherto been believed that the horny cells of the epidermis have no nuclei. This is, however,

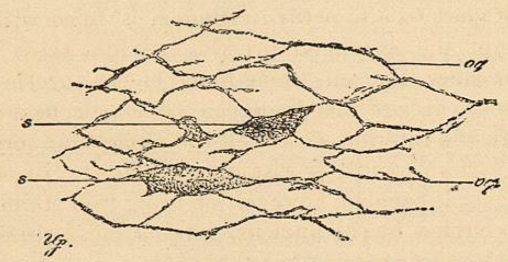

FIG. 6.—Thin vertical section through fresh horny layer from the sole of the foot. Complete digestion by trypsin. *o q*, optical cross-sections of the horny membranes in contact by means of fine prickles; *s*, pieces of the horny membranes seen from the side.

not absolutely correct, as I showed in 1875. The nuclei of the epidermis do not disappear by being dissolved, but by desiccation, shrinking and crumbling, and traces of them can, therefore, still be found in the upper part of the horny layer. On sections half digested in an acid solution, there can be seen in the incised horny cells remains of the cell-body stretched like a veil between the horny membrane and the remains of the nucleus.

The fact that we find *the type of an animal cell-membrane* reproduced in the cornified cells of the epidermis demonstrates the necessity of coloring only *thin sections* if we wish to obtain good, uniform stainings. Thus horny cells entirely or partially cut through are stained red by picro-carmin, whereas whole ones turn yellow.

If double and triple stainings are employed, the most brilliant cell-mosaic may be obtained on sections not quite thin enough, to which no importance should, however, be attached, although such an appearance has puzzled many an observer.

From this fact many important conclusions may be drawn, bearing upon pathological changes in the horny substance. Just as the swelling up of the horny cells in dilute alkaline solutions[1] is really a swelling up of the cell-contents, which passively distends the membrane into a globular shape; enormous distentions, with the formation of medullary cavities, etc., also occur very frequently in the fully developed horny substance. No plausible explanation of this phenomenon has as yet been advanced. Here the alterations in *the contents of the horny cells* take place under the influence of the alkaline tissue-fluid. *The densest horny masses do not consist of solid horny substance, but of a honeycomb-like horny frame-work.*

Ranvier was the first to call attention to the fact that, in treating the epidermis with hyperosmic

[1] This fact also explains the curious phenomenon that the horny cells swell up much more rapidly in dilute than in concentrated alkalies. The horny membranes are but slightly affected by alkalies and acids, but are readily permeable by water. For this reason dilute alkalies gain access to the contents of the cells much more readily than concentrated alkalies.

acid, a lower stratum of the horny layer (three to five cells thick) assumes an intensely deep-black color, like that of the horny cells which were in direct contact with the acid on the surface and sides of the specimen, whereas a middle layer of horny cells remains white, "if the action of the acid were not too intense." This observer explained the peculiar appearance of the black border around osmium specimens by the difficult penetration of the acid from all sides into the horny layer. I showed that this explanation was unsatisfactory, and that one lower zone of horny layer really has a strong elective affinity for osmic acid. Ranvier, in the latest number of his "Traité technique," makes a very noteworthy attempt to explain the different appearances. He says that the human skin normally contains fat, which explains its blackening by osmium, which does not occur if the horny layer is previously deprived of its fat by absolute alcohol; for the same reason the first row of cells above the granular layer, which contain no fat, on account of the presence of water, do not take on the osmium staining. It will be seen from what follows, that the statement of Ranvier that fat plays a part in the staining of the horny cells by osmium, is, in fact, correct, but that the conditions under which this occurs are of a very complicated nature, and that further investigation of this subject may throw much light upon the constitution of the horny layer.

Table Showing the most Important Color-reactions for the Horny Layer of the Palm of the Hand.

Names of the layers of the epidermis.		Consistence.	Hyperosmic acid. Containing fat.	Hyperosmic acid. No fat.	Picro-carmin.	Hæmatoxylin (glacial acetic acid).	Iodine-violet (but little decolorized).	Salicylated chloride of iron (after H. Hebra).
A. Horny layer (Stratum corneum).	1. Sup'rficial	Dense..	Black....	Light....	Yellow.	Bluishwhite	Blue..	Brown.
	2. Middle...	Loose..	Light.....	D'k brown	Red....	Violet.....		Light.
	3. Superbas'l	Dense..	Black..	Light...	D'k red.	Bluish-white.	Light...	Light br'wn not constant.
	4. Basal (str. lucidum Oehl) 4 *a*.	Very dense.			Yellow.		Blue..	
	4 *b*.		Light....	D'k brown		Granules.		
B. Granular layer (Stratum granulosum).		Soft, near B dens'r	Protoplasm stained (green).			Stained violet.	Nuclei stained (blue).	Brown.
C. Prickle layer (Strat. spinosum).	Rete (Malpighi). Germinal layer Flemming.				Nuclei stained (dark red).	Nuclei stained (blue).		Light brown.

We find that the horny layer presents four different strata, which I shall designate the superficial (or terminal) layer, 2. the middle layer, 3. the superbasal, 4. the basal horny layer. The basal horny layer, to judge from its reaction with osmium, comprises two or more very distinct subdivisions, which are always present. In the preceding table, I have distinguished these as 4 *a* and 4 *b*. The basal horny layer is the hardest, the connection between the cells being somewhat less firm in

the superbasal layer, and much less so in the middle layer. The superficial terminal layer is more firmly constructed and harder than the two latter. It will be at once seen from a study of the next two columns of the table *that the action of osmium upon the horny layer cannot be regarded as identical with its action upon fatty bodies.* If it were, the acid would have no effect whatever after removal of the fat, *i. e.*, all four divisions of the horny layer would retain their light color. Instead of this, the remarkable fact becomes manifest that, in consequence of the preceding thorough removal of the fat (by treatment for weeks with ether constantly renewed), complete inversion of the osmium staining takes place, so that zones 1, 3, and 4 *a*, which otherwise would be turned black remain light, after removal of the fat, whereas, on the other hand, 2 and 4 *b*, which in fresh skin are not affected by the acid, assume an intense brown color after being freed from fat. The action of the acid upon epidermis deprived of its fat is the same, whether this has been accomplished by ether or by absolute alcohol. This fact is very difficult of explanation, and cannot be reconciled with the view that osmic acid only marks out the distribution of the fat in the epidermis. The most singular thing about these reactions is evidently the splitting up of the basal horny layer, Oehl's stratum lucidum, into two subdivisions, the lower of which contains only one row of cells,[1] the upper from three to five, and which, even in the smallest space, shows the above-mentioned inversion. Just as the osmic acid proves that the basal horny layer is composed of two entirely distinct layers, so the results of staining with picro-carmin and iodine-violet render necessary the recognition of a special layer between the hard basal and the middle softer horny layer. This I have called the superbasal layer, and have shown that it passes along the sweat pores nearly to the surface of the horny layer, forming rings around them. Hæmatoxylin has but little effect upon either the basal or the superbasal horny layer (see table). In specimens stained with hæmatoxylin, however, the basal horny layer seems narrowed from below, the row of cells, 4 *b*, being wanting. This appearance is due to the fact that the remains of granules which can still be found in it are stained by the agent, and, therefore, the entire layer seems to be a part of the deeper-seated granular layer. The superficial firmer horny layer, in staining with picro-carmin, hæmatoxylin, and iodine-violet, shows the same colors as the firm basal horny layer, while the softer middle layer is differently stained by each of the first two of these agents. In deep staining with iodine-violet, the whole superficial and middle horny layer is blue; if the specimen be decolorized, a row of horizontal white bands appears here alternating with blue. The broadest of these and the first to appear is our superbasal layer. Those which show themselves later and higher up, show that the same process which passes from the basal to the superbasal horny layer begins still more frequently within the horny layer, and, therefore, that the whole range of variations in color is due to entirely mechanical causes. It is, in fact, a physical necessity that, beginning with the basal horny layer, which covers the whole surface of the body like a dense horny cloak, changes should take place externally in the other horny layers. For while new horny cells are added from within to the basal layer, the outer ones are spread over a larger area, and stretched and loosened by the surface tension. The horny membranes must necessarily become thinned, and the intercellular spaces widened, in order that the fat may more readily penetrate into the skin. Whether these mechanical relations alone suffice to explain the inversion of the osmium-staining, I must leave undetermined. But as the horny cells possess only a limited degree of elasticity, this tension cannot continue indefinitely; when they can no longer yield to it, they must again constitute a denser layer, a few rows of cells higher up, and compress those which follow them. For this reason, light and colored bands alternate in sections stained with iodine-violet, and the same process ultimately leads to the formation of the dense superficial terminal layer, in which aid is furnished by the factor of atmospheric desiccation. If this terminal layer be further stretched, it ruptures, and the cells are cast off in horizontal scales.

[1] This layer, 4 *b*, was formerly described by me, after the usual osmium reaction, as the "clear" layer (1875), but I at the same time stated that the stratum lucidum of Oehl comprised the two layers 4 *a* and 4 *b* (see table). In spite of this fact, Ranvier his recently (probably by an oversight) identified this (my former "clear" layer) with Oehl's stratum lucidum. The stratum lucidum is that layer containing from four to six rows of cells, which on fresh unstained sections attracts the attention by its transparency above the prickle and granular layers. As my former "clear" layer can be found only after the uninverted osmium staining, and as such special names should be avoided, I now abandon it entirely. Oehl's stratum lucidum should also be dropped as an inexact term, and also because it does not require a special name, it being only a portion of the horny layer.

The thickness of the entire horny layer, aside from that of the underlying prickle-layer, is therefore dependent upon only two factors: 1. The quantity of the bridge-like connecting threads, and 2. their density and elasticity after their conversion into horny substance.

If we take a connected view of these histological facts, we are already in a position to form a morphological, even if not a chemico-physiological notion of the nature of the process of cornification. Ever since the appearance of the work of Langerhans on the granular layer, there has been a great deal of fascination in the view that a factor had been found in the granules of this layer which controls the process of cornification, since we could either regard them as already formed drops of horny substance, or at least as an intermediate product between albumin and keratin.

Signification of Keratohyalin for the Process of Cornification.—The former view was adopted by Zabludowski for the cornification of the bills of birds, while Waldeyer, who found keratohyalin also in the medulla of the hair, the hoof of the horse, and the claws of ruminants, thinks it very probable that a close connection exists between this substance and the process of cornification. For the internal root-sheath, he imagines "that the keratohyalin once formed gradually becomes reunited with the protoplasmic network within which it originated or was deposited, and that the horny substance is the result of this union." This renewed solution of the keratohyalin in the protoplasm of the cells seems very probable, to judge from the microscopic apppearances. *The true cornification of the cells of the epidermis, however, affects only the outer layer of the cell, and consists in the formation of a horny membrane.* We have already seen that the contents of the horny cells are just as readily digested by pepsin (and trypsin) as keratohyalin before it has been redissolved in the former. We cannot, therefore, say that either the former or the latter is *cornified*. *Cornification is a process which takes place in the epidermis, and is entirely confined to the periphery of the cells and their protoplasmic connecting threads.* The changes which take place in the interior of the cells, particularly the appearance of keratohyalin, are secondary phenomena which have a bearing upon cell life in general, but not upon cornification.

The statement thus made about the epidermis is in perfect harmony with our experience concerning keratohyalin in other respects. It is supported by the capriciousness exhibited by this substance in the various places in which it is found. We sometimes find it in large quantities, but occupying a limited space just below the point of complete cornification (epidermis), and sometimes, long before this process begins, in higher layers (internal root-sheath); in many places (variola, vaccine process), in which a high degree of cornification is reached, it is entirely wanting, or almost entirely, and, on the other hand, we find it in large masses in places where cornification is very incomplete. We must, however, also recognize the fact that this substance should not be regarded simply as the result of a senile change in the cells of the epidermis, for it does not appear in the external root-sheath which so long remains unproductive. *Therefore the appearance of keratohyalin, although an accessory phenomenon of the process of cornification, is really produced by the latter, which affects the periphery of the cell, not vice versa, the appearance of keratohyalin leads to cornification.* Peripheral cornification of cells without the appearance of keratohyalin frequently takes place, as was just intimated. These statements refer, in the first place, only to cornification of the cells of the epidermis, and it is possible that subsequent examinations of other kinds of epithelium during the process of cornification may demonstrate the presence of horny material in the interior of the cells, perhaps as a horny frame-work.

Development of the Nail.—Embryos of two or three months seem at the first glance to be already provided with nails. A more careful examination shows, however, that no true nail exists; the posterior and lateral folds and the free border are wanting; the impression of a nail plate is due to the circumstance that the surface of the last phalanges of the fingers and toes is smoother and more shining than the rest of the skin, and, without forming a distinct wall, is more firmly united to the underlying tissues. At this time (see Fig. 7, 1), the epidermis of the toe consists of several layers of epithelium; the undermost, beautiful cylindrical cells; above them two or three rows of prickle-cells, and over all a few layers of horny cells, without intervening granular cells. Only on the dorsal surface of the ungual phalanx is there an altered epithelium upon a surface bounded anteriorly by a groove (*r*) running across the tip of the finger, and posteriorly by a depression in the epithelium which runs obliquely inwards and backwards. This entire portion of the skin is closely united with the cartilaginous end phalanx by means of a firm and relatively mature connective tissue. It is covered by a cubical epithelium, a thin prickle layer, and a thick lamellated horny layer. The last passes from the dorsum of the second phalanx over the oblique epithelial ridge and the entire end phalanx, and gives to the skin of the latter its horny character. It extends beyond the anterior groove, and becomes inserted into the tip of the finger.

In the study of comparative anatomy, we meet with several instances of such partial cornification. One was described by Welcker in the sloth, under the name of "epitrichium," as a membrane covering the hairy coat of the animal like a second amnion, which is afterwards cast off. It was more correctly described by Kölliker as the horny layer of a former fœtal period. Welcker had in mind the fact that the epitrichium is transformed into the nail of the sloth. In the case of the fœtus of the hog, I can vouch for the conversion of the epitrichium, which is also present there, into the embryonic hoof, and hence I believe that in the human fœtus also the above-described horny layer of the ungual phalanx would pass into an epitrichium covering the whole skin if the horny layer in general had a firmer consistency. In the human subject, however, a trace of the horny layer of the first fœtal months remains only on the ungual phalanx till a later period, and to this, in imitation of Welcker's term, I have given the name "*eponychium*," and also for the reason that the subsequent nail really comes out from under this peculiar horny covering. During the whole of life, we find a small horny plate at the posterior nail-fold, which passes down from the back of the finger upon the nail, and, if it becomes adherent to the latter, gives rise to lacerations of the horny layer of the back of the finger. For this reason, we are in the habit of keeping it carefully separated from the nail. This plate is the indistinct residue of the fœtal eponychium.

Fig. 7, II. represents the toe of a fœtus of four and a half months. The distal phalanx has much increased in size on the flexor aspect where the skin is loosely attached to the phalanx; at this point the so-called "pulp" of the (fingers and) toes is formed. We find the first papillæ and epithelial processes, but only in places where the connective tissue is loose, *i. e.*, back of the posterior epithelial ridge and below and in front of the anterior groove. No epithelial process is developed on the dorsum of the phalanx. In this way *three entirely different regions are marked out on the distal phalanx of the toe,* which steadily become more distinct; that behind the epithelial ridge, as the nail-wall, the sterile middle portion as the subsequent nail-bed, and that before the groove as the pulp of the toe; the posterior epithelial ridge is at once recognizable as the subsequent nail-fold. It is easy to see that it is the firm eponychium which, passing from the nail-wall to the pulp of the toe, hinders the free development of all the tissues underneath it. Under this firm horny covering there arises at about this time *the first trace of the definitive nail,* in the shape of a small lenticular collection of large transparent prickle cells at the orifice of the nail-fold (see Fig. 7, II., *n*).

In Fig. 7, III., which illustrates a longitudinal section of a toe of six months, the definitive nail (*n*) has already attained larger dimensions, the large transparent cells having penetrated further backwards into the nail-fold, and pushed themselves forward under the eponychium, becoming meanwhile cornified from before backwards, as can be recognized from their assuming a yellow tint when stained with picro-carmin. Granular cells do not appear during this process, for which reason no white transitional zone can be recognized macroscopically. The nail-fold, like the nail-bed, still retains its cubical

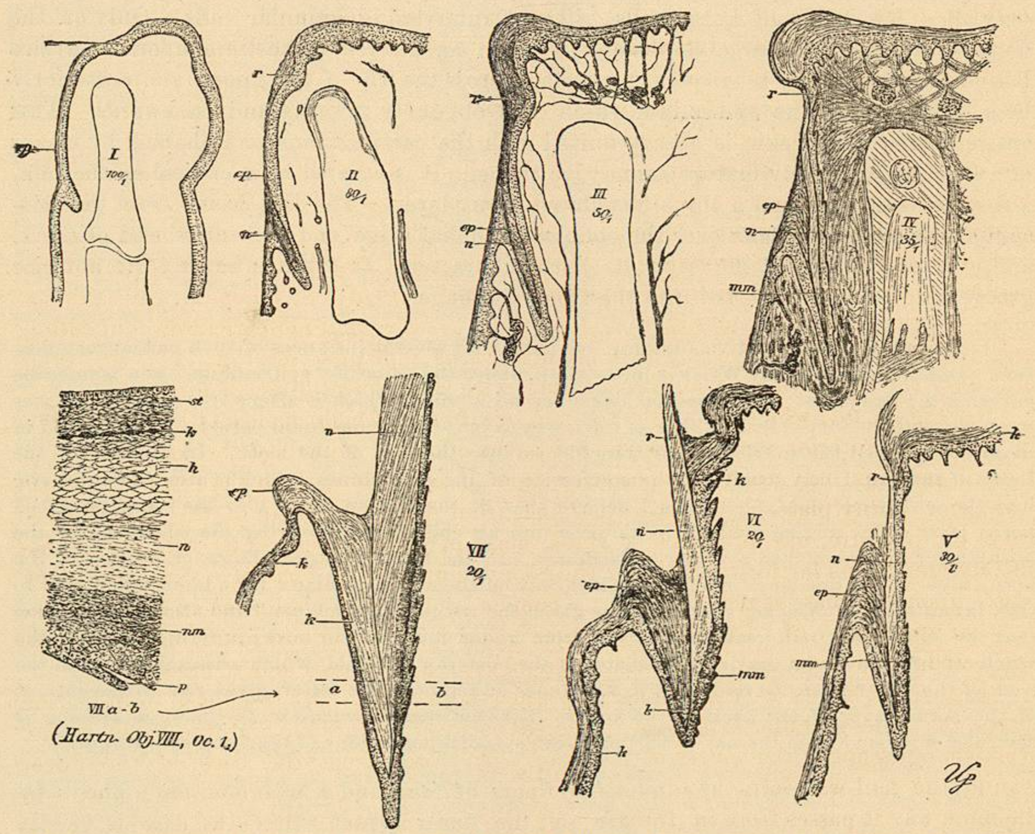

FIG. 7.—Development of the toe-nail.—I. 3d month, *e p*, eponychium ; *r*, upper groove ; II. 4½ months ; *n*, rudiment of nail. III. 6 months ; IV. 8 months ; *n*, *m*, matrix of nail. V. at birth ; *k*, granular layer. VI. child 3 weeks old. VII. child 3 years old. VIII. *a b*, section *a b*, from VII. magnified ; *s t*, prickle-layer of roof of nail-fold; *k*, granular layer of roof of nail-fold ; *h*, horny-layer of roof of nail-fold ; *n*, nail ; *n m*, matrix of nail ; *p*, papilla of matrix of nail.

epithelium, the outer rows of which are everywhere arranged perpendicularly to the surface of the corium. The mature nail-cells push themselves in between the prickle and horny layers of the nail-bed, and slowly progress forwards. The nail-wall and the pulp of the toe have at this time already sent out numerous epithelial cones and coil-glands into the loose connective tissue, and the slowness of the development of the region of the nail becomes more and more striking. The nail-fold, although it has nearly doubled in size, no longer reaches posteriorly as far as the condyles of the phalanx, nor does the upper epithelial groove reach the pulp of the finger anteriorly, but is pushed by the steady growth of the phalanx back upon its dorsum, being still held in close con-

tact with the nail-wall by the eponychium. At this time the further shaping of the connective-tissue surroundings of the nail has made progress. The two lateral digital arteries give off two transverse anastomosing vascular loops, corresponding exactly to the epithelial ridge and the anterior groove. The nail-bed is supplied by these with very fine arterial capillaries, which empty into broad venous ones. The bundles of fibrillæ which constitute the nail-bed originate from the periosteum of the under side of the end phalanx (see Fig. 7, IV.), and spread out over the head of the phalanx in the form of a broad fan, towards the pulp of the toe and upwards and backwards towards the whole nail-bed. On the tip of the toe these fibres are crossed obliquely by others, which come from the anterior part of the nail-region, and thus very wide meshes are formed at this point, in which coil-glands and lobules of fat are inclosed. At the posterior part of the nail-bed, the last fibres of the fan bend over towards the periosteum of the upper side of the phalanx, in consequence of which the connective tissue near the nail-border becomes less dense. The nail-fold is surrounded by bundles of fibres which are cut across in making longitudinal sections, and are seen around the horse-shoe-shaped nail-fold, running at right angles to the axis of the toe. This arrangement of the fibrous bundles of the corium enables us to comprehend : in the first place, that the anterior portion of the nail-bed is closely united with the anterior flattened part of the phalanx, while the posterior portion, and still more the nail-fold, have a softer and more yielding foundation, and that the epithelial cones which are afterwards sent out (see Fig. 7, V., VI., VII.), all follow the course of the connective tissue, with their apices directed forwards.

In Fig. 7, IV., which shows the toe-nail of a fœtus of eight months, the eponychium in its entire anterior portion has yielded to the efforts at growth of the parts around it. It still remains only upon the posterior part of the true nail, in the form of a broad "anterior horny plate." We see that the front part of the tip of the finger, freed from its pressure, has produced a thick mass of horny layer. The nail, which has already crept thus far forwards under the eponychium, in the form of a very thin plate, passes upon this mass as a delicate horny lamella, and we now obtain macroscopically the peculiar appearance of a free nail, no longer covered by the eponychium, which still has no free edge, however, but terminates in front upon a transverse horny mass.

Fig. 6, V., shows us the toe-nail of a new-born child. Microscopical examination shows that the granular layer has appeared between the prickle and the horny layers, everywhere except at the border of the nail. It passes from the back of the finger around the nail-wall into the hindmost corner of the nail-fold, where it terminates. In the same way it passes from in front under the nail as far as this is unattached to the skin, and here also it suddenly disappears. Epithelial proliferation also takes place at this time upon the nail-bed freed from pressure, by which numerous cones are sent out in the direction of the pulp of the toe. On macroscopical examination a characteristic change is seen. The anterior transverse horny mass already described becomes torn through in the middle layers, and scales off until the normal level is reached. In consequence of this the nail, which has crept forwards over it, now stands exposed in the form of that irregular edge, thin as paper which usually falls a victim to soap and water during the first few days after birth.

Fig. 7, VI., represents the toe-nail of a child three weeks old. The epithelial cones of the nail-bed have grown still larger. At the bottom of the nail three or four papillæ, which were faintly marked near the end of fœtal life, have become greatly developed. Their growth is intimately associated with the increased production of nail-substance which now goes on over the whole bottom of the nail-fold. The fully-formed nail has,