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THE MODIFIED PLASMA MEMBRANES OF THE TRANSITION AND HORNY CELLS IN NORMAL HUMAN EPIDERMIS AS REVEALED BY ELECTRON MICROSCOPY

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In repeated electron-microscopic studies of different types of epidermis and mucous membrane a broad zone has been demonstrated at the surfaces of the cells in stratum corneum (10, 14, 16, 17, 18, 19, 20, 21, 23, 24). The question of how this broad zone is formed has not yet been settled. Brody (1, 2, 3) observed that the broad zone of the transition (T-) and horny cells at its outer face was bounded by an opaque layer. This, he assumed, might possibly correspond to the plasma membrane in other tissues. Since it was not possible to judge whether both the inner broad zone and the outer opaque layer belonged to the plasma membrane, or if the former represented a condensation of the cytoplasm immediately adjacent to the plasma membrane, Brody (1) suggested the term "cell boundary" for the two layers together. Zelickson (27) thought that the broad zone was the result of a fusion of the outer and inner leaflets of the plasma membrane of the non-cornified cells. Matoltsy *et al.* (18, 19) and Matoltsy (17) suggest that the so-called membrane-coating granules (18) fuse with the plasma membrane of the stratum-intermedium cells. After the fusion, the granules are assumed to empty their content into the intercellular space, and the "thickened and coated cell envelopes" of the horny cells are thought to be formed by a spreading of this content over the cell surface (17, 18, 19). This view has been supported by some authors (14, 25), whereas other investigators have questioned the hypothesis (5, 7, 11, 13, 21, 26). In rat transitional epithelium Hicks (15) suggests that the Golgi complex is involved in the synthesis of the thick cell membrane.

In other studies of amphibian skin (12), normal human epidermis (5, 6, 7), rat-tongue epithelium (11) and human cervical squamous epithelium (13) it has been clearly demonstrated that the T- and horny cells are bounded by an outer, triple-layered membrane which corresponds to the plasma membrane of the non-cornified cells. The broad zone appears immediately adjacent to the intracytoplasmic face of the inner leaflet of the triple-layered membrane. Farquhar *et al.* (12) and Farbman (11) regard the broad zone as a shell of condensed cytoplasm.

In normal human epidermis it has been shown that the broad zone is delimited from the cytoplasm by a thin, opaque layer (4). On the strength of this observation Brody (7) has suggested that the T- and horny cells are bounded by a modified plasma membrane, comprising the outer triple-layered membrane (here referred to

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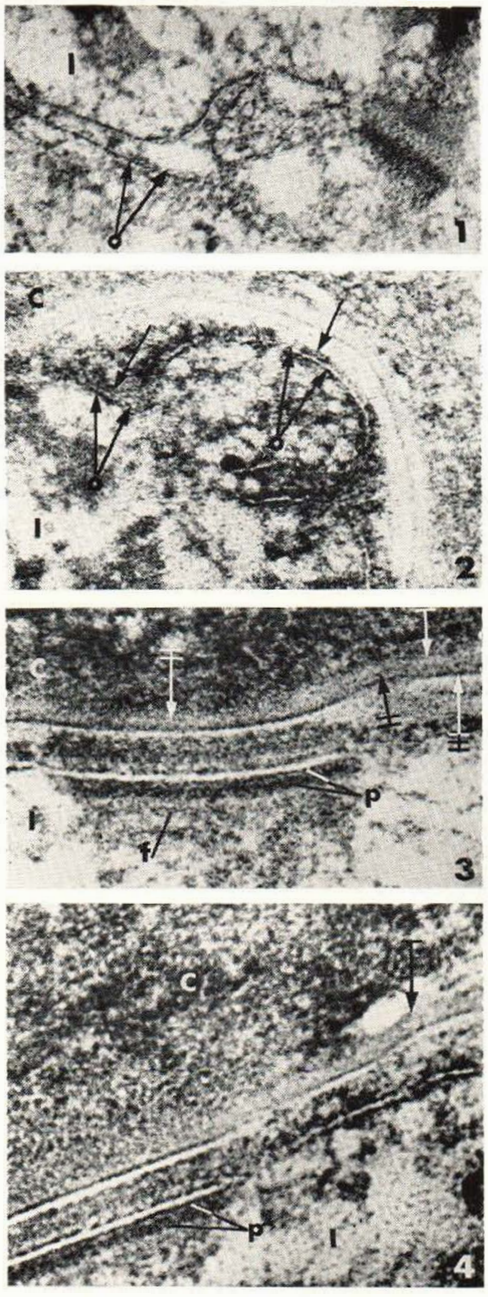


Fig. 1. Cells in the lower stratum intermedium. ×68,000.

Figs. 2–4. Transition between strata intermedium and corneum. ×113,000, 159,000 and 159,000 respectively.

The plasma membrane (o→) shows in the cells of the stratum intermedium (I) an asymmetric, triple-layered pattern. Close to the plasma membrane of the stratum-intermedium cells facing the horny cells (C) different intercellular components (→) occur which, however, are often distinctly separated from the asymmetric plasma membrane (o→). The opaque plaque (p) of the regular desmosomes in the stratum-intermedium cells (I) has a layered structure: it is bounded by an inner, thin, opaque layer and between the latter and the inner leaflet of the plasma membrane are distinguished two less opaque layers separated by a more opaque layer. The broad zone of the horny cells (C) is towards the cytoplasm bounded by a thin, opaque layer (|→). Between this and the opaque inner leaflet (|-|-|-→) of the plasma membrane proper an opaque layer (|-|-→) is faintly visible in the broad zone. f, filamentous striation into which the filaments insert.

as the "plasma membrane proper") and the inner broad zone, including the thin, inner opaque layer which delimits the broad zone from the cytoplasm. Rupec (22) and Brody (6, 7) have demonstrated that the plaques of the regular desmosomes in the non-cornified epidermis have a layered structure. The inner opaque layer of the plaques can sometimes be recognized outside the regular desmosomes (6). A generally held notion is that the very opaque plaques of the regular desmosomes in the non-cornified epidermis are no longer discernible or only faintly indicated in the horny cells. On the basis of these various observations a more detailed study has been made of the plasma membranes in normal human epidermis, and particularly of the broad zones of the modified plasma membranes of the T- and horny cells.

Material and Methods

For Material and Methods the reader is referred to an earlier paper (6). The tissue has been examined in an RCA EMU 3 A and a Philips EM 300 electron microscope. scope.

Results

Non-cornified epidermis

The plasma membranes of the non-cornified cells, except those of the stratum-intermedium cells facing the T- and horny cells, show everywhere an asymmetric, triple-layered pattern (Figs. 1 and 17). The

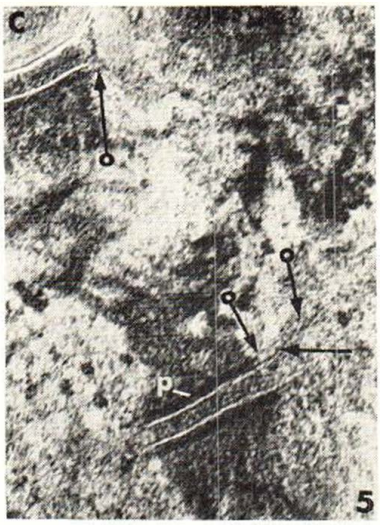


Fig. 5. Cells in the upper stratum intermedium. The thin, opaque layer forming the inner limit of the plaques (p) of the regular desmosomes continues outside the desmosomal areas. It (o→) runs here parallel to the inner leaflet (→) of the plasma membrane. C, horny cell. ×85,000 .

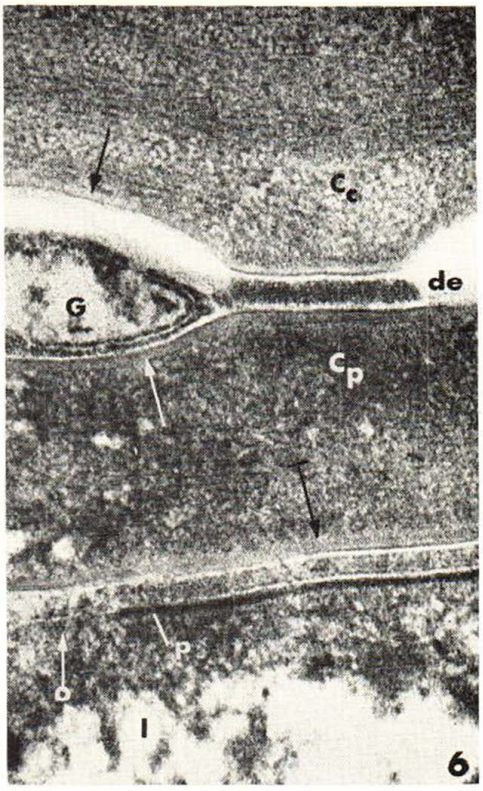


Fig. 6. The opaque plaque-component (p) in the stratum-intermedium cell (I) continues outside the regular desmosome. Outside the desmosome it (o→) appears less opaque. In the completely cornified cell (C_c) the broad zone (→) displays a uniformly stained, continuous layer of low opacity and passes without a break through the regular desmosome (de). The broad zone (→) of the partially cornified cell (C_p) has an opacity between that of the plaque in the stratum-intermedium cell (I) and that of the broad zone in the completely cornified cell (C_c). In the partially cornified cell (C_p) the fibrils are separated from the broad zone within the desmosomes by a narrow, less opaque layer (|→). Close to the latter the fibrils appear rather opaque. G, granule in the intercellular space. ×113,000.

plasma membrane consists of an opaque, inner leaflet, a light, intermediate layer and a less opaque, outer leaflet. Within the regular desmosomes the inner and outer leaflets are more opaque than between the desmosomes but retain a similar asymmetry with respect to opacity (Figs. 5 and 17). The plasma membrane has a total thickness of about 80 Å.

The plasma membranes of the cells in the stratum intermedium facing the T- and horny cells display in some areas a distinct asymmetric pattern, while in others they appear symmetric. Higher magnification of the areas in which the plasma membrane exhibits a symmetric staining often reveal a thin, opaque layer appearing outside of and close to the outer, less opaque leaflet of the plasma membrane (Fig. 2). This finding may perhaps indicate that the symmetric staining of the plasma membrane may sometimes be due to the closeness of intercellular components to the outer leaflet.

The plaques of the regular desmosomes are very opaque throughout the non-cornified epidermis (Fig. 5). This high opacity characterizes also the plaques of the regular desmosomes in the stratum-intermedium cells at the transition to the T- and horny cells (Figs. 3–6, 9, 10, 13, 15 and 16). The plaques have a layered structure (Figs. 3, 4 and 17). A thin, opaque layer forms the inner limit of the plaques. Between this

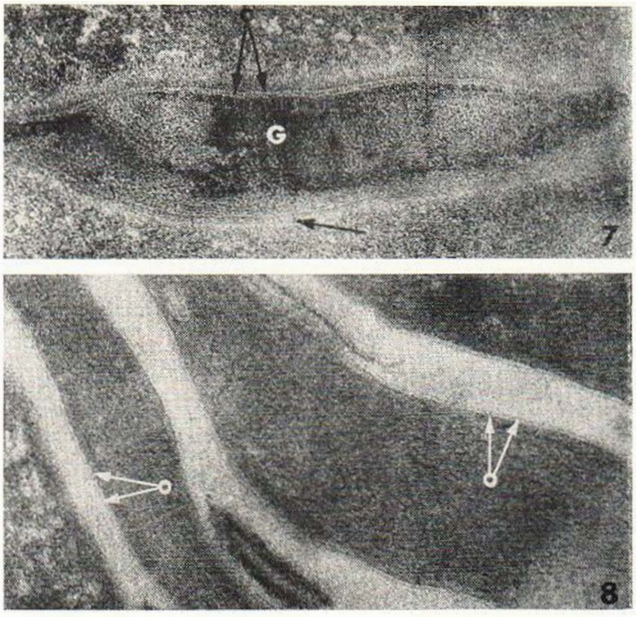


Fig. 7. Cells in the superficial layer of the stratum corneum. ×84,000.
Fig. 8. Cells in the basal layer of the stratum corneum. ×84,000.

The asymmetric, triple-layered plasma membrane proper (o→) appears distinctly. Immediately adjacent to the inner leaflet of the latter the broad zone (→) is faintly discernible. The granule (G) occupying the intercellular space is clearly separated from the outer leaflet of the plasma membrane proper by a narrow, less opaque layer.

and the inner leaflet of the plasma membrane two somewhat less opaque layers are observed separated by a more opaque layer. The latter three layers are responsible for the high opacity of the plaques. The total thickness of the plaque varies between 100 and 120 Å.

The thin, opaque layer which forms the inner limit of the plaques may quite often be followed for varying distances into the cytoplasm beyond the regular desmosomes. It appears here as a thin, opaque layer running parallel to the inner leaflet of the plasma membrane (Fig. 5). The area between this layer (here called "cytoplasmic layer") and the inner leaflet of the plasma membrane has mostly the same low opacity as the cytoplasm outside the cytoplasmic layer. Occosionally the opacity between the latter and the inner leaflet of the plasma membrane is increased (Fig. 6). Here the plaque-component of the regular desmosomes seems to continue outside the desmosomal area. This part of the plaque exhibits the same thickness as that within the regular desmosome but is less opaque.

The fibrils insert into a filamentous striation (Figs. 3, 4, 6, 13 and 17). This runs parallel to the plaques but is separated from the latter by a less opaque, narrow layer. Close to the filamentous striation the fibrils often show high opacity.

T- and horny cells

In uranyl-acetate staining alone the outer leaflet of the plasma membrane proper of the T- and horny cells is mostly very faintly stained or not recognized at all. In combined uranyl-acetate and lead-tartrate staining the outer leaflet is for the most part distinctly discernible. However, irrespectively of the type of staining, whenever the plasma membrane proper of the T- and horny cells appears triple-layered, it always shows an asymmetric pattern (Figs. 7, 8 and 17). The membrane consists of an opaque, inner leaflet, a light, intermediate layer and a less opaque, outer leaflet. The

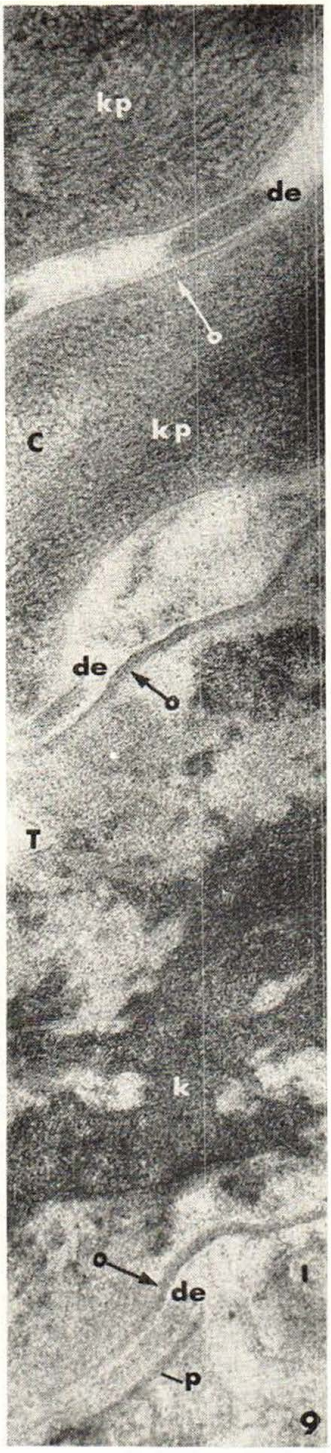
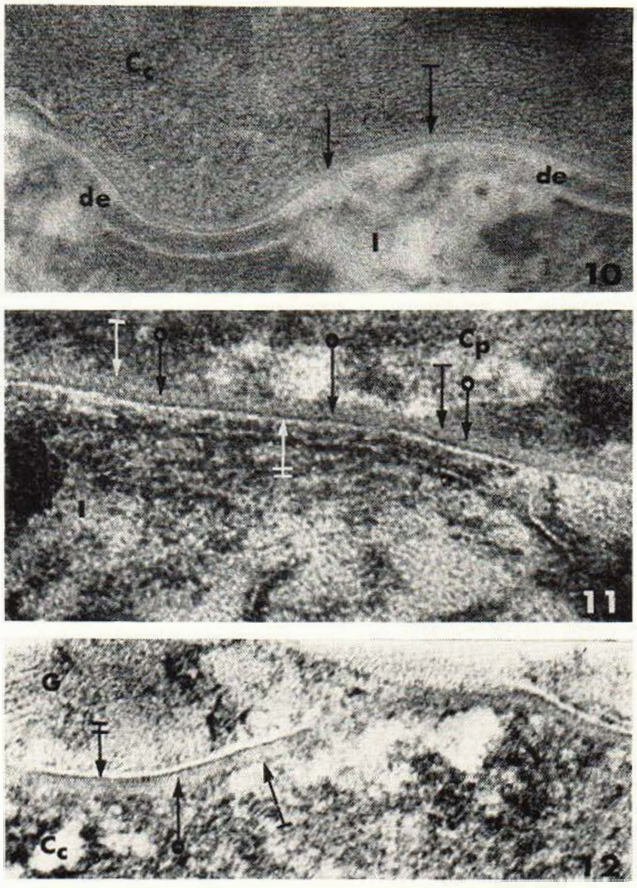


Fig. 9. The broad zones (o→) of the T- (T) and horny (C) cells show a continuous layer and pass through the regular desmosomes (de) without a break. In the T-cell (T) the broad zone outside the desmosomes has about the same high opacity as the plaque (p) of the regular desmosome in the stratum-intermedium cell (I), whereas within the desmosomes the broad zone is only faintly stained. In the horny cells (C) the broad zones are uniformly stained and have low opacity. k, keratohyalin. kp, keratin pattern. ×84,000.

inner and outer leaflets are more opaque in the regular desmosomes than between them but retain a similar asymmetry in opacity (Figs. 6, 10, 14 and 17). The plasma membrane proper has a total thickness of about 80 Å.

Immediately adjacent to the intracytoplasmic face of the inner leaflet of the plasma membrane proper the broad zone occurs. It forms here a continuous layer and passes without a break through the regular desmosomes (Figs. 3, 6, 9, 10 and 13–17). The broad zone is delimited from the cytoplasm by a thin, opaque layer (Figs. 3, 4, 6, 9–12, 14 and 17). The layer between the latter and the inner leaflet of the plasma membrane proper has been termed the "inner broad intermediate layer" (7). This layer shows here indications of a stratification with two less opaque layers separated by a more opaque layer (Figs. 3, 11, 12 and 17). The inner broad intermediate layer displays the same stratification also within the regular desmosomes (Figs. 13, 14 and 17). In the T- and horny cells the total thickness of the broad zone varies between 100 and 120 Å.

The inner broad intermediate layer is responsible for the opacity of the broad zone. Outside the desmosomal areas the inner broad intermediate layer of the T-cells has about the same high opacity as the plaques of the regular desmosomes in the non-cornified epidermis (Figs. 9, 15 and 16). Within the desmosomes the inner broad intermediate layer of the T-cells usually has very low opacity compared to that of the plaques in the non-cornified epidermis. In the completely cornified cells, whether they occur close to the stratum intermedium or at any level of the stratum corneum, the inner broad intermediate layer shows throughout its entire length a uniform, low opacity (Figs. 6, 9 and 10).



Figs. 10–12. Transition between strata intermedium (I) and corneum. ×84,000, 140,000 and 132,000 respectively.

The broad zone (→) of the completely cornified cell (C_c) shows a uniformly stained, continuous layer of low opacity. It passes through the regular desmosomes (de) without a break. Towards the cytoplasm the broad zone is bounded by a thin, opaque layer (|→). In the partially cornified (C_p) and in the completely cornified (C_c) cell a faintly visible opaque layer (o→) appears in the broad zone between the inner opaque layer (|→) and the inner opaque leaflet (|-|→) of the plasma membrane proper. G, granule in the intercellular space.

An intermediate stage in opacity is constituted by the inner broad intermediate layer of the so-called partially cornified cell (Fig. 6). This cell-type has not earlier been described in electron-microscopic studies. It represents a cornified cell which still contains clearly visible keratohyalin (8).

Within the regular desmosomes the fibrils do not insert into the broad zones but are separated from the latter by a narrow, less opaque layer (Figs. 6, 15 and 17). Close to this narrow, less opaque layer the fibrils are often more opaque than the rest of the fibrillar substance in the T- and horny cells. Occasionally a filamentous striation is faintly discernible (Fig. 16).

Discussion

The present study of the normal human epidermis reveals that the T- and horny cells are bounded by a modified plasma membrane, comprising an outer, about 80 Å thick, asymmetric, triple-layered plasma membrane proper and an inner, broad zone, which varies between 100 and 120 Å in

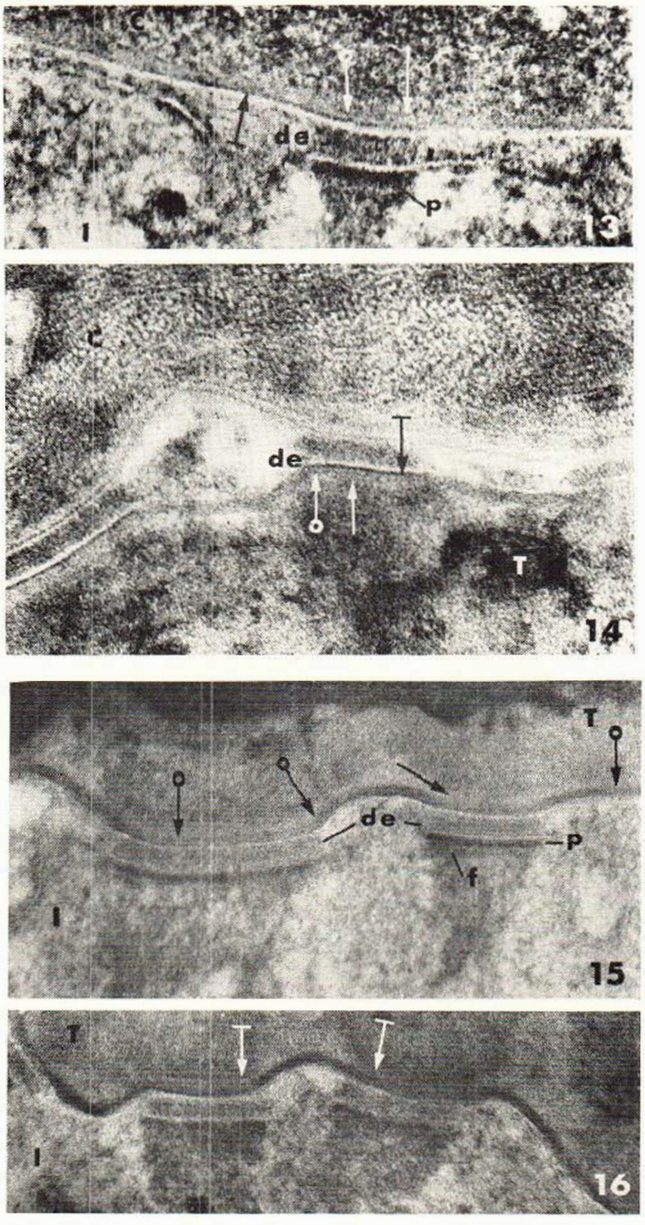


Fig. 13. Transition between a stratum-intermedium (I) and a horny (C) cell. ×140,000.
Fig. 14. Transition between a T- (T) and horny (C) cell. ×95,000.

Within the regular desmosomes (de) the broad zones display a layered structure. An opaque layer (→) forms the inner limit of the broad zones. Between the latter and the opaque, inner leaflet (|→) of the plasma membrane proper a faintly visible opaque layer (o→) appears in the broad zone. p, plaque.

Figs. 15 and 16. The broad zone (o→) of the T-cells (T) forms a continuous layer and passes without a break through the regular desmosomes (de). Outside the desmosomes it has about the same high opacity as that of the plaques (p) of the regular desmosomes in the stratum-intermedium cells (I), whereas within the desmosomes the broad zone is only faintly stained. In the desmosomes the fibrils in the T-cells (T) are separated from the broad zone by a narrow, less opaque layer (→). Occasionally, a faintly visible filamentous striation (|→) appears, into which the filaments insert. f, filamentous striation in the regular desmosome in the stratum-intermedium cell (I). ×84,000.

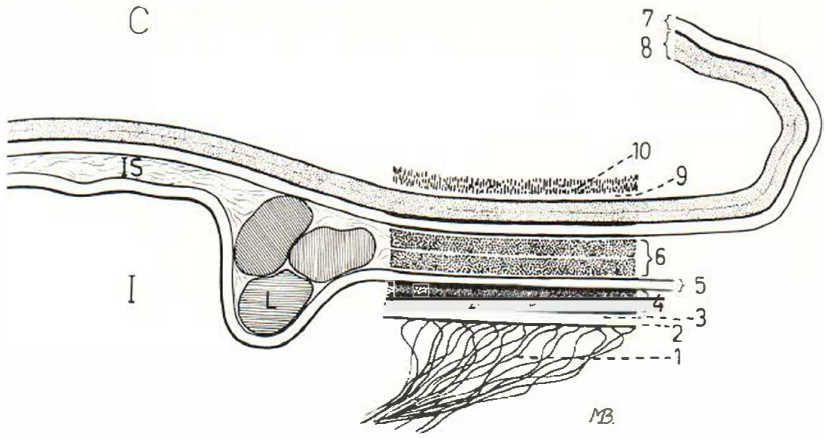


Fig. 17. Schematic drawing of the fine structure of the plasma membrane in a stratum-intermedium cell (I), of the modified plasma membrane in a horny cell (C) and of a regular desmosome. (For text see also references 6 and 7.)

In the regular desmosome of the non-cornified epidermis the filaments (1) insert into a filamentous striation (2) which runs parallel to the plaque (4) but is separated from the latter by a narrow, less opaque layer (3). The opaque plaque (4) has a layered structure: a thin, opaque layer constitutes its inner limit; between the latter and the opaque, inner leaflet of the plasma membrane (5) occur two somewhat less opaque layers separated by a more opaque layer. The plasma membrane (5) exhibits an asymmetric, triple-layered pattern with an opaque, inner leaflet, a light, intermediate layer and a less opaque, outer leaflet.

The intercellular component (6) of the regular desmosome has a layered structure (for text see reference 6).

The modified plasma membrane of the horny cell comprises an outer, asymmetric, triple-layered plasma membrane proper (7) and an inner, broad zone (8). The plasma membrane proper consists of a less opaque, outer leaflet, a light, intermediate layer and an opaque, inner leaflet. The inner and outer leaflets of the plasma membrane proper (7) and of the plasma membrane (5) are more opaque within than between the regular desmosomes but retain a similar asymmetry in opacity. Immediately adjacent to the opaque, inner leaflet of the plasma membrane proper (7) the broad zone (8) occurs. This displays the same stratification as the plaque (4) of the regular desmosome in the stratum-intermedium cell (I). The fibrils (10) in the horny cell (C) are in the regular desmosomes separated from the broad zone by a narrow, less opaque layer (9). IS, intercellular space containing different components, among others lysosomes (L) (cf. references 7 and 26).

thickness. In ultrastructure and thickness the plasma membrane proper corresponds to the plasma membrane of the non-cornified epidermis (4). The observation of an asymmetric pattern of the plasma membrane proper is in agreement with the findings in earlier studies on the normal human epidermis (5, 6, 7). Farquhar *et al.* (11), investigating amphibian skin, Farbman (10), investigating rat-tongue epithelium, and Grubb *et al.* (13), investigating human cervical squamous epithelium, have also demonstrated an outer, triple-layered plasma membrane of the horny cells. This membrane shows, however, a symmetric pattern both in the amphibian epidermis and in the rat-tongue epithelium. In the amphibian epidermis it attains a thickness of about 100 Å (12). In the rat-tongue epithelium its outer leaflet appears fragmented (11).

In the present material the broad zone of the modified plasma membrane forms a continuous layer along the entire intracytoplasmic face of the inner leaflet of the plasma membrane proper, with the same thickness in the T- and horny cells. In the present study, as in an earlier investigation (4), it is found that the broad zone is de-

limited from the cytoplasm by a thin, opaque layer. It has here been further observed that the inner broad intermediate layer (7) exhibits indications of a stratification with two less opaque layers separated by a more opaque layer. The same ultrastructure which is here described for the broad zones of the modified plasma membranes of the T-, and the partially cornified (8) and completely cornified cells has by Rupec (22) and Brody (6, 7) earlier been described for the plaques of the regular desmosomes in the non-cornified epidermis. The two components also agree in thickness.

No plaques are formed in the so-called junctional desmosomes occurring along the dermo-epidermal junction (6, 7). Plaques are first seen in the desmosomal structures occurring along the lateral and distal surfaces of the basal cells, where they are very opaque. They are also distinctly recognized at all surfaces of the cells in the strata spinosum and intermedium. It emerges from what has been said above that the plaques of the regular desmosomes coincide completely, in the T- and horny cells, in regard both to thickness and ultrastructure, with the broad zones between the desmosomes. Concerning opacity, however, they are still clearly distinguishable in the T-cells: the inner broad intermediate layer within the regular desmosomes displays much less opacity than that outside the desmosomes, which latter has about the same high opacity as the plaques of the regular desmosomes in the non-cornified epidermis. In the partially cornified cells (8) there seems to be a 'levelling' of the opacity of the inner broad intermediate layer within and outside the regular desmosomes. In the completely cornified cell this levelling is complete, which results in the appearance of a uniformly stained, inner broad intermediate layer of rather low opacity. The identical morphologic picture of the plaques of the regular desmosomes in the non-cornified epidermis and of the broad zones of the modified plasma membranes in the T- and horny cells suggest that we are here dealing with similar structures. The changes in the opacity of the two components may possibly also indicate similar alterations in their chemical composition.

Outside the regular desmosomes in the non-cornified epidermis one can often follow the thin, opaque layer forming the inner limit of the plaque (6) and corresponding to the inner, opaque layer of the broad zone. In the cytoplasm this layer is parallel to the inner leaflet of the plasma membrane. In the present material a more opaque substance has occasionally been observed between the cytoplasmic layer and the inner leaflet of the plasma membrane, suggesting a continuation of the plaque-component outside the regular desmosomes. These observations may perhaps imply a similar formation of the plaques and the broad zones, *viz.* through the deposition of a stratified structure between the cytoplasmic layer and the inner leaflet of the plasma membrane. The formation of these components seems to presuppose a certain degree of differentiation of the epidermis (9).

In accordance with earlier observations in the non-cornified epidermis (3, 6, 7, 22) this study shows that the filaments in the T- and horny cells do not within the regular desmosomes insert into the broad zones of the modified plasma membranes but are separated from the latter by a narrow, less opaque layer. Both the junctional and the regular desmosomes in the non-cornified epidermis contain a filamentous striation into which the filaments insert (6, 7). Separated by a narrow, less opaque layer this striation runs parallel to the inner leaflet of the plasma membrane in the junctional desmosomes and parallel to the plaques in the regular desmosomes. In the present material a filamentous striation appears only faintly discernible in the T- and horny cells. Close to the narrow, less opaque layer which separates the fibrils from the broad zones, the fibrils may often exhibit higher opacity than the rest of the fibrillar substance in the cells. Similar increased opacity is also shown by the fibrils close to the filamentous striation in the non-cornified epidermis.

Even if, at the present stage, it is diffi-

cult to say anything with certainty about the function of the broad zone of the modified plasma membranes of the T- and horny cells, it is tempting to speculate on its role in the physiology and morphology of skin. The stratum corneum is, as compared with other tissues of the body, unusually tough and unyielding in spite of its considerable elasticity. Apparently the cells of the horny layer are held together by forces which are probably developed to a considerably lesser degree in other tissues of the human body. In view of these considerations it does not seem unreasonable to assume that the broad zones form a kind of cement in these cellular layers enhancing the coherence of the cells, thus providing a structural basis for the highly specialized functional characteristics of the skin.

SUMMARY

This paper is a presentation of the ultrastructure of the modified plasma membranes of the T- and horny cells in normal human epidermis from the abdominal, upper-arm and sacral regions.

The modified plasma membranes have the same thickness in the T-cells and in the partially and completely cornified cells. They consist of an outer, about 80 Å thick, asymmetric, triple-layered plasma membrane proper and an inner, 100 to 120 Å thick, continuous broad zone.

The plasma membrane proper corresponds in thickness, ultrastructure and opacity with the plasma membrane of the non-cornified cells.

The broad zone displays a layered structure. With respect to thickness and ultrastructure it agrees with the plaques of the regular desmosomes in the non-cornified epidermis.

Outside the regular desmosomes the inner broad intermediate layer of the T-cells has about the same high opacity as the corresponding layer of the plaques in the regular desmosomes of non-cornified epidermis, whereas within the desmosomes the inner broad intermediate layer shows very low opacity. In the partially cornified cells there seems to be a 'levelling' of the opacity of the inner broad intermediate layer within and outside the desmosomes. In the completely cornified cells this levelling is complete, and one finds here a continuous, uniformly stained inner broad intermediate layer of low opacity.

In the non-cornified epidermis the thin, opaque layer forming the inner limit of the plaques is often seen to continue outside the regular desmosomes. In the cytoplasm this cytoplasmic layer runs parallel to the inner leaflet of the plasma membrane. Occasionally one observes increased opacity of the area between the two latter layers, indicating a continuation of the plaque-component outside the desmosomes.

Within the desmosomes filaments do not insert into the broad zones in the T- and horny cells, but are separated from these by a narrow, less opaque layer. A filamentous striation is only faintly indicated.

An attempt has been made to interpret the possible role of the broad zone of the modified plasma membranes in the function of the skin.

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