THE JOURNAL OF INVESTIGATIVE DERMATOLOGY
Vol. 60, No. 1

Printed in U.S.A.

THE MERKEL CELL*

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ABSTRACT

The Merkel cell is a distinctive cell normally found in the epidermis of mammals. It possesses a folded nucleus; a clear, organelle-rich cytoplasm with peripheral protrusions among the epithelial cells; and a few desmosomal attachments to adjacent cells. The cytoplasm is characterized by many dense-cored, membrane-bound granules, 80 to 100 nm in diameter and distributed in the cytoplasm next to the nerve termination. The Merkel cell is found isolated in the epidermis or associated with epithelial nerve endings such as the hederiform ending of Merkel–Ranvier, the tactile hair disk of Pinkus, and the organ of Eimer. It may be observed in the dermis in relation to nerve trunks and also within the corpuscles of Grandry found in the skin of the duck bill. The Merkel cell appears to be an individual cell type, probably derived from the neural crest, which is capable of living in union with neural and epithelial cells. The Merkel cell penetrates the epidermis in fetal life and functions as a specific, slowly adapting, sensory touch receptor.

In 1875, Merkel described a unique epidermal cell with a specific innervation that he believed to be a special sensory cell of the skin [1]. He named this structure a "Tastzellen" to indicate his belief that it was an end-organ for touch sensation and to account for its location in the skin of all areas of the body. Merkel's description, made from osmium-prepared tissue, led to confusion between the Merkel cell and the melanocyte because both are clear cells by ordinary light microscopic and neurohistologic techniques [2]. However, the melanocyte does not have innervation, and contrasts to the Merkel cell which with its special myelinated nerve supply is mainly confined to specialized areas of the skin. Weddell and colleagues believed Merkel cells were artifacts [3], and Hagen [4] in 1965 reviewed sensory receptors without reference to them. The purpose of our review is to bring together the classic and the more recent ultrastructural observations about the Merkel cell to serve as a basis for continuing studies of its biology and responsiveness.

LIGHT MICROSCOPY

The Merkel cell was first demonstrated by the nonspecific osmic acid technique in which small blocks of tissue were stained for 24 hours. Myelinated nerves were also demonstrated by this technique. Ranvier [5] used a gold chloride technique to demonstrate similar cells in the epidermis of the pig snout. Although the Langerhans cell stains with gold techniques, Ranvier's preparations clearly demonstrated Merkel cells and not high-level intra-epidermal, dendritic cells. Botezat [6], Boeke [7], and Winkelmann [8] each has demonstrated Merkel cells by silver methods, which discriminate among the melanocytes, Langerhans cells, and the innervated Merkel cell of glabrous skin (Fig. 1 *Top*). The methylene blue techniques utilized by Retzius [9], Dogiel [10], and Miller and associates [11] also demonstrate the Merkel cell and its innervation but do not distinguish it from other intra-epithelial dendritic cells. None of these techniques demonstrates the cell itself but show the expanded intra-epithelial axon tip, which is associated with the specialized cell (Fig. 1 *Bottom*). The specialized cell is observed only as a clear halo about the stained axon disk.

The advent of ultrastructural techniques demonstrated that a special cell within the epidermis was related to the expanded nerve ending. The methodology required is routine, involving glutaraldehyde fixation, osmium postfixation, and uranyl or lead staining of the tissue.

ELECTRON MICROSCOPY

The ultrastructure of the Merkel cell is distinctive for its clear cytoplasm, lobulated nucleus, specific granule, and innervation. The cell is commonly situated in the basal layer of the epidermis and is the same size or slightly larger than the associated keratinocytes (Fig. 2). It is usually oval or rounded, but may be elongated or flattened [12]. Occasionally, the Merkel cell bulges toward the dermis, but the nerve ending or keratinocyte cytoplasm usually separates it from the epithelial basement membrane. Short, spine-like protrusions of the plasma membrane, with a cytoplasmic core, indent the surrounding keratinocytes, and thicker processes may insinuate among them. The Merkel cell is attached to adjacent keratinocytes by desmosomes, and although filaments are present on the cytoplasmic aspects of these desmosomes and are sparsely distributed elsewhere in the cytoplasm, they are many fewer in number, and finer, than the tonofilaments of the keratinocytes [13]. This relative sparsity of

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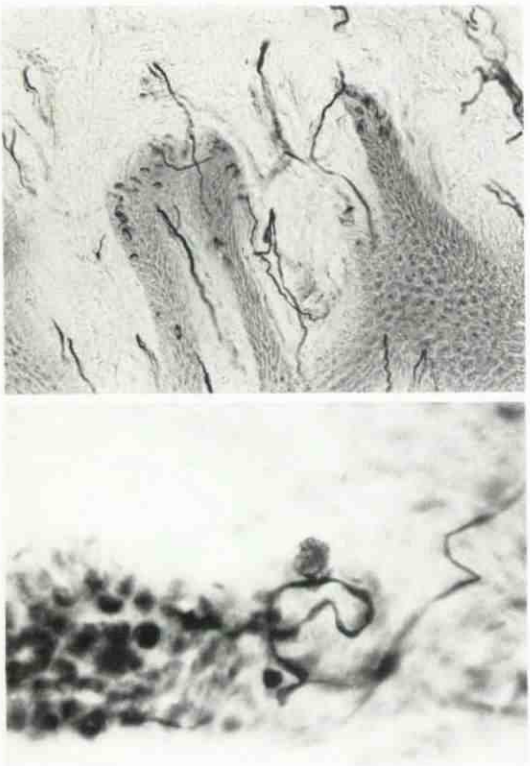

FIG. 1. *Top:* Intra-epithelial Merkel cells and their myelinated innervation in palate of kangaroo. (Winkelmann silver method; × 174.) *Bottom:* Expanded nerve disk at base of Merkel cell in human digital epidermis. (Winkelmann silver method, × 241.) (From Winkelmann RK: Nerve Endings in Normal and Pathologic Skin: Contributions to the Anatomy of Sensation. Springfield, Illinois, Charles C Thomas, Publisher, 1960. By permission.)

filaments results in the cytoplasm of the Merkel cell appearing "clear" in comparison with that of the keratinocyte. Hemidesmosomes have not been described in association with the basal plasma membrane of Merkel cells in fully developed epidermis, though Hashimoto [14] has illustrated them in the fetus. The rough endoplasmic reticulum is usually poorly developed, but free ribosomes are numerous. Rare centrioles have been described. The mitochondria may be large or small, elongated or short, depending on the species studied. Golgi membranes and vesicles are present, but not prominent. Cytoplasmic vesicles, multivesicular bodies, and large dense lysosomal-like granules have been described, and glycogen particles are usually observed. Mature melanin granules within a membrane can be found; Langerhans cell granules and partially melanized melanosomes are not present. Most of these cytoplasmic structures are found above the nucleus.

The nucleus of the Merkel cell is highly lobulated, and the nucleus and cell are oriented horizontally in the epidermis, with the long axis of the cell parallel to the surface of the epidermis. No unique structures of the nucleus have been found.

The specific Merkel cell granule is an electron-dense granule smaller than and distinct from any other special epidermal cell organelle (Fig. 3 *Top*). The size of the granules may vary from 70 to 180 nm in diameter but commonly range from 80 to 100 nm. The granules possess a dense core surrounded by a clear space. The membrane is separated from the core by a clear space of 8 nm. The size and appearance of the granules are identical in mouse, dog, cat, and human skin. The granules are concentrated in the cytoplasmic space below the Merkel cell nucleus, opposite the nerve termination and remote from the Golgi region. Occasionally, granules are observed elsewhere in the cell, but the striking nerve-associated polarity of these Merkel granules is common to the cell in all species and in all circumstances examined to date.

The terminal axon, which is closely associated with the dermal face of the Merkel cell, is derived from myelinated nerve. The myelinated nerve fiber loses its myelin sheath close to the epidermis and continues onward as an unmyelinated axon surrounded by Schwann cell cytoplasm and basement membrane. The fiber terminates as a flat meniscus filled with mitochondria and both dense and clear vesicles. It directly contacts the basal aspect of the Merkel cell, the basement membrane of the axon fusing with the basal lamina of the epidermis. Smith [15] noted that the axon does not penetrate the epidermis proper, but intra-epidermal axonal processes may be seen in contact with nonbasal segments of the plasma membrane of the cell, particularly in the fetus. No special modification of the apposed membranes of cell and axon has been described, and characteristic synaptic vesicles have not been observed within the Merkel cell. Rare Merkel cells, without associated nerve terminals, are observed in gingiva. Pederson and Winkelmann* described a cell that was without desmosomes or a nerve ending but one that contained the Merkel granule (Fig. 3 *Bottom*).

The finding of cytofilaments within the Merkel cell, and the presence of desmosomes along the plasma membrane, suggested that the cell was a highly specialized and modified epidermal keratinocyte. However, recent ultrastructural studies of fetal skin indicate a different developmental origin.

While Munger [16] mentioned a light response to periodic acid-Schiff staining (PAS) and whereas Kasprzak et al [17] used Bouin-fixed PAS tissue to count Merkel cells, no other unique light microscopic or ultramicroscopic techniques for histochemical demonstration of the Merkel cell exist.

* Unpublished study.

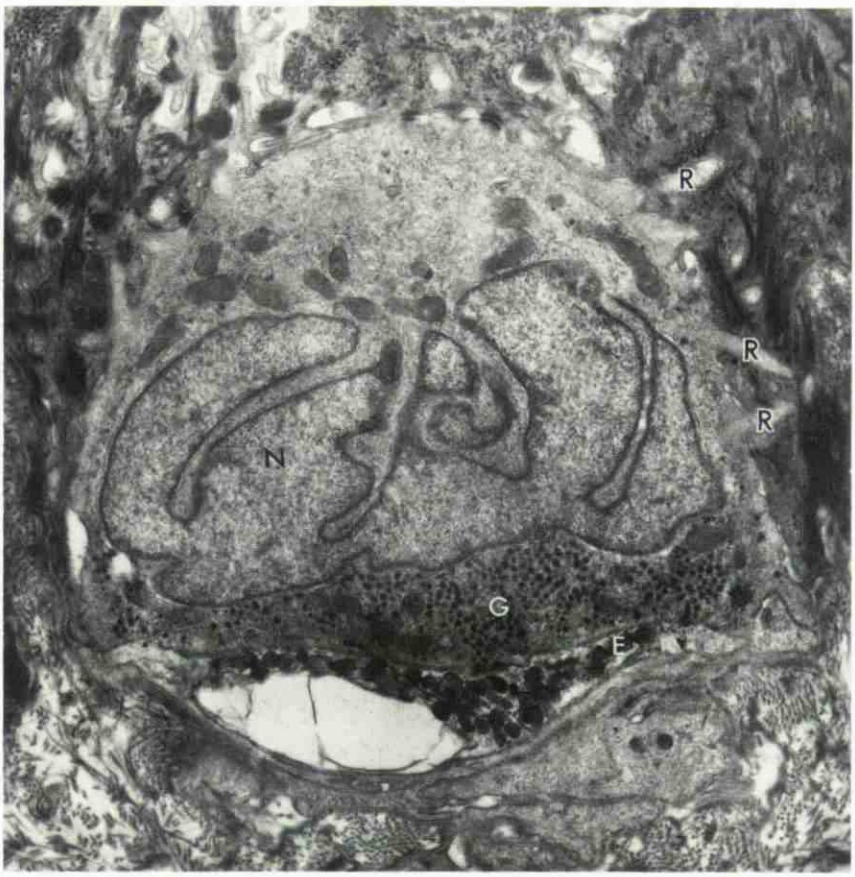

FIG. 2. Typical Merkel cell in epithelium of tactile hair disk of cat skin. (× 13,920.) *N*, nucleus; *G*, granules; *E*, nerve ending; *R*, spinous rootfeet of cytoplasm. (Courtesy of Dr. A. Iggo.)

DISTRIBUTION AND FREQUENCY

The Merkel cell may be observed in epidermis of both haired and glabrous skin and occasionally in the dermis. A representation of the occurrence of this cell is found in the Table. The end-organ has been found in the skin of mammals in the tactile hair disk of Pinkus. It has been readily found in the distal glabrous skin of fingers and paws in the hederiform ending of Merkel–Ranvier. It is typically observed in the nasal skin of most mammals and is associated with additional intra-epithelial neurofibrils. In the mole, shrew, and opossum, such an apparatus is organized into a complex nerve ending, the end-organ of Eimer. The Merkel cell is observed in the lip, gingiva, and palatal rugae of animals and man. The cell may be observed nestled into the external root sheath of the vibrissal or sinus hair or whisker of mammals. The discovery of the cell in the dermis, associated or unassociated with nerve tissue, will be described in detail.

Merkel cells may be found in clusters in the distal or central glabrous skin of the mammals studied. The cells are more frequent and dense in the skin of small structures; thus, they are more dense in finger than in toe skin epidermis; they are more dense in the skin of children than of adults. Winkelmann [8] stated that in human skin the cell was observed only in distal glabrous skin, but we now recognize its presence in the tactile hair disk of Pinkus and in the human palate. Recently, Hashimoto [24] noted the Merkel cell in human gingiva. Specific information demonstrating the presence of the cells in the skin of man, baboon, monkey, dog, mole, cat, shrew, kangaroo, opossum, rabbit, rat, and mouse is available. The cells are dense in the most dis-

TABLE

Merkel Cell Nerve Endings

Epithelial
Hederiform (Ranvier [18], Eimer [19])
Tactile hair disk (Pinkus [20, 21])
Without nerve (Pederson and Winkelmann*)
Hair sheath
Vibrissal or sensory hair
Dermal
Simple (Breathnach [22, 23])
Grandry corpuscle

* Unpublished study.

tal, hairless skin of man and become less frequent toward the dorsal and haired portions of the digits. Dogiel [25] observed Merkel cells in the nail bed, but Martino [26], Vitali [27], and Winkelmann [8] did not. The cells are certainly present in the nail bed of the human fetus [14]. The principal area for these cells in human skin is in the tactile hair disk.

DEVELOPMENT

Pérez and Pérez [28] and Jałowy [29] identified Merkel cells by silver technique in human fetal

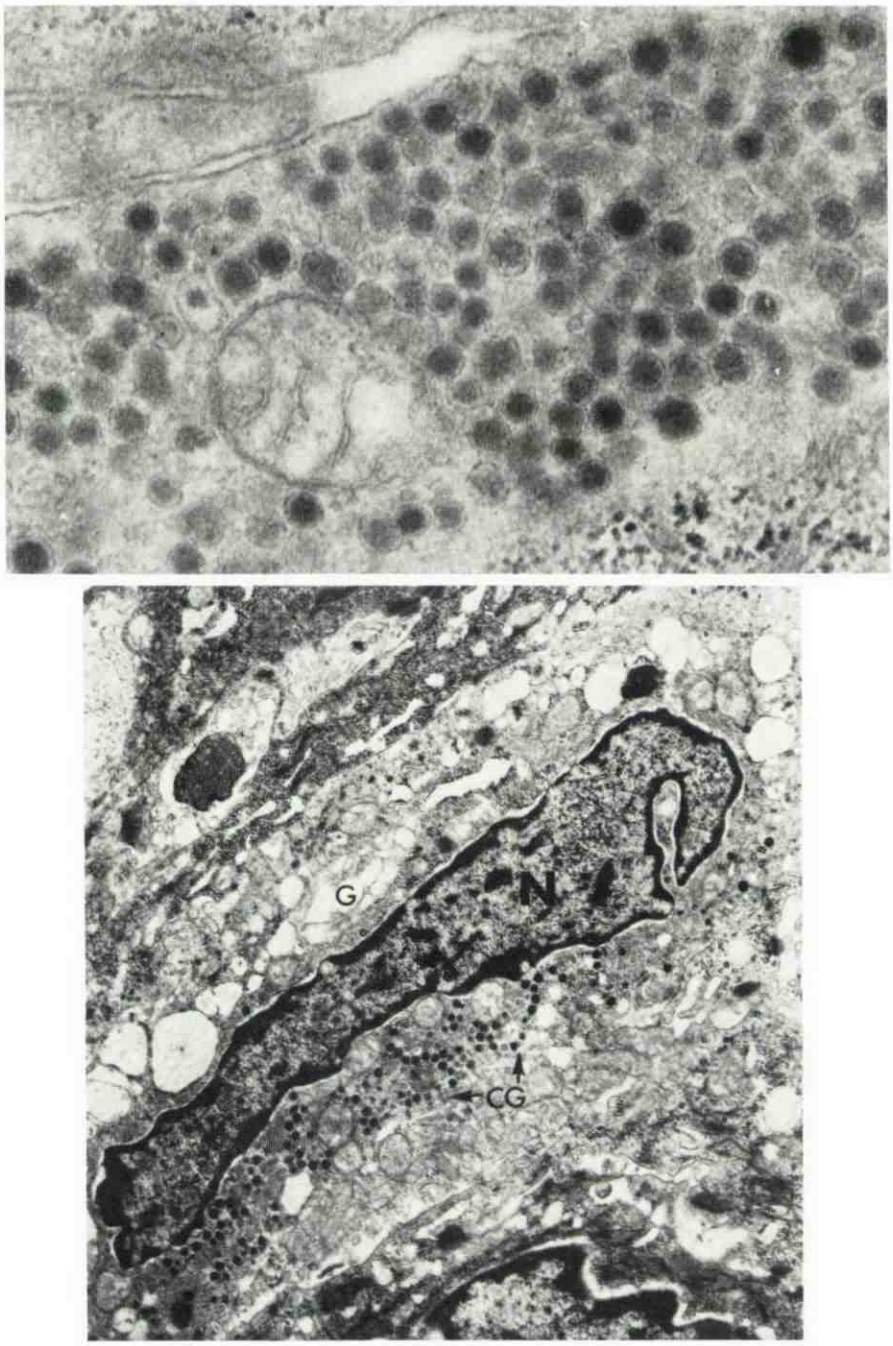

FIG. 3. *Top:* Characteristic granules in cytoplasm of Merkel cell from outer root sheath of human fetal hair follicle. Granules have dense core separated from the limiting membrane by a more electron-translucent interval. (× 62,310.) (Micrograph supplied by Mrs. E. Robins.) *Bottom:* Merkel cell from human gingiva with specific Merkel granules but without desmosomes or nerve endings. (× 22,785.) *N*, nucleus; *G*, granules; *CG*, dense core of Merkel granules.

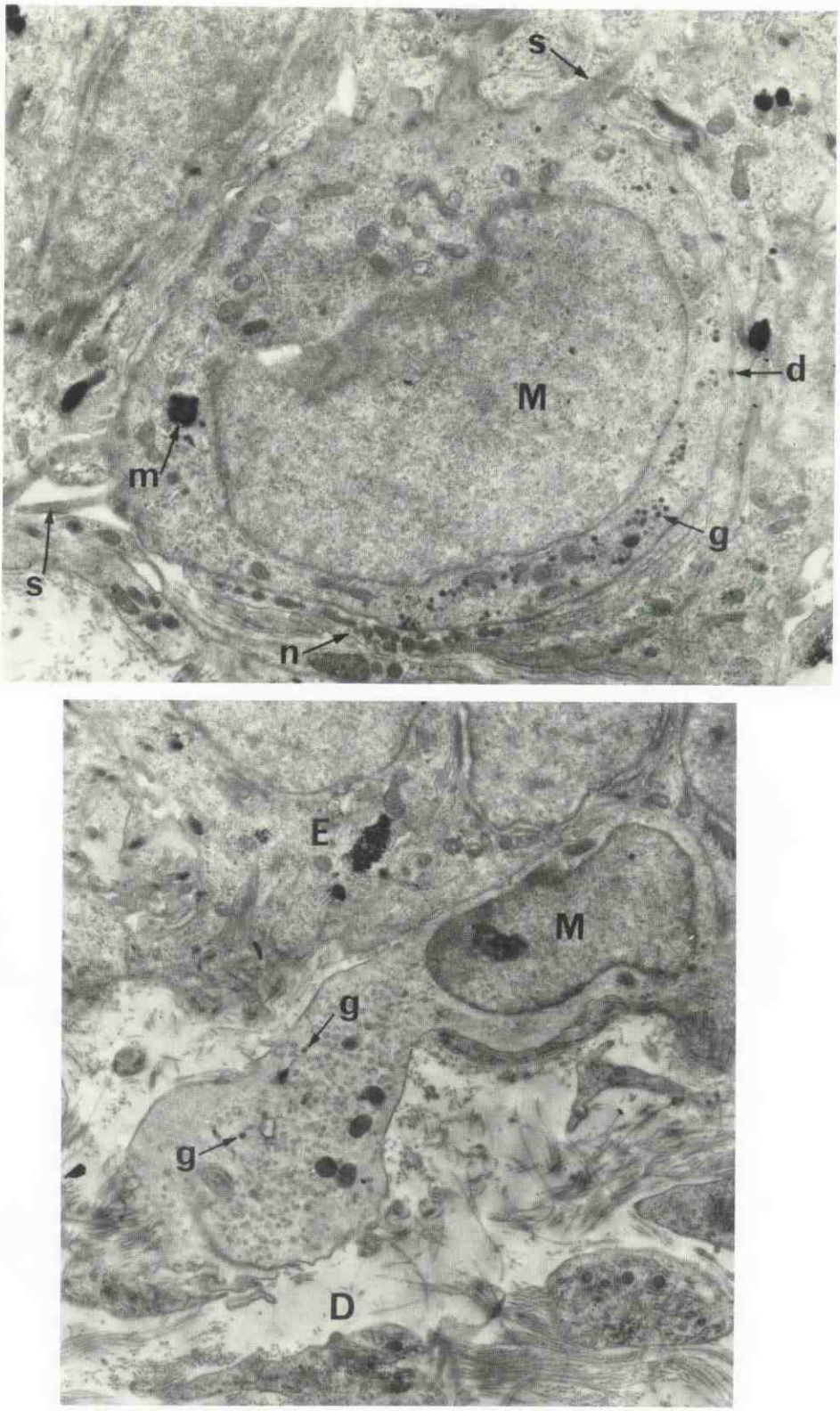

FIG. 4. *Top:* Merkel cell (*M*) in basal layer of epidermis of finger of human fetus: *d*, desmosome; *g*, characteristic granules; *m*, compound melanosome in cytoplasm; *n*, neurite (axon) with many mitochondria in contact with basal plasma membrane of Merkel cell; *s*, spine-like protrusion of plasma membrane. (× 12,006.) *Bottom:* Merkel cell (*M*) from finger of human fetus. Cell is in process of passing from dermis (*D*) into epidermis (*E*). Portion of cell containing nucleus is already in epidermis. In that portion of cell still lying in dermis, a few fully differentiated granules (*g*) may be seen. Other small vesicles may represent formative stages of granules. (× 7,830.)

epidermis at the seventh month of intra-uterine life. Breathnach and Robins [30] and Breathnach [22, 23], using electron microscopy, noted their presence as early as the 16th week in the outer root sheath of the hair follicle and in the finger tip. These human fetal Merkel cells had essentially the same but simpler ultrastructural features as those of mature epidermis (Fig. 4 *Top*). This latter feature was also noted by Lyne and Hollis [31] in fetal sheep epidermis. Breathnach and Robins [30] also reported the presence of Merkel cells in the dermis, frequently associated with Schwann-cell axonal complexes, and their apparent passage across the epidermal-dermal junction (Fig. 4 *Bottom*). These latter observations, together with the observation that at any stage of development Merkel cells differ significantly in morphology from adjacent keratinocytes, and the failure to observe any cell that could be regarded as a transitional or intermediate form, led Breathnach [22, 23] to conclude that the Merkel cell could not be regarded as a modified keratinocyte. The evidence suggests, rather, that the cell migrates from the dermis into the epidermis during fetal life and that it may be of Schwann-cell or of neural-crest origin. These observations on the human fetus have been confirmed recently by Hashimoto [14], who also agrees with the suggestion [23] that the specific granules of the Merkel cell may stem from the Golgi apparatus. However, this view has only circumstantial evidence to support it. In the mature Merkel cell, the characteristic granules are mainly concentrated on the side of the nucleus, away from the space occupied by the Golgi apparatus.

These developmental studies give added relevance to McGavran's isolated report of a single "chromaffin" cell in human dermis [32]. This was evidently a Merkel cell, perhaps fallen by the wayside, on its way to the epidermis.

Tactile disks are readily observed in newborn cat skin and are at their greatest density, 200/sq cm [33]. During the first month of life, the number per unit area decreases steadily. The tactile pad is 120 μ in diameter at birth and, by 49 days, reaches 200 μ, the lower range of normal in the adult. The number of Merkel cells is small, as assessed by periodic acid–Schiff stain, until 11 days of age when a rapid increase in number occurs.

THE TACTILE HAIR DISK

The tactile hair disk (Haarscheibe) was described by Pinkus [20, 21] in a study of human skin and the skin of many mammals. The hair disk of Pinkus is an epithelial thickening observed near the hair follicle. Its external surface may have a slightly rounded eminence, and frequently the disk can be recognized because the round or polygonal eminence interrupts the normal skin markings. In some mammals, the disk is vascularized and, with a drop of oil to clear the stratum corneum, the distinctive epithelial neural unit can be recognized by the cluster of blood vessels [33]. The hair disk does not occur with every hair follicle. Kawamura [34] proposed that about every fifth hair on the human trunk was associated with a hair disk. Kamide† found one to every four hair follicles. In cats the hair disk has no constant relation to the hair follicle [33]; in many mammals the disks are caudal to the hair [35], but in man their position is not consistent [36–38]. More recent morphologic observations by Straile [39] have led to the use of the term "tylotriche pad" to describe the hair disk, whereas Iggo and Muir [33] used the term "touch dome." We believe the term "hair disk" is simple, adequately descriptive, and has the advantage of tradition, despite the variable relation to the hair follicle.

Smith [15, 40] found that in human skin the hair disk was 0.3 to 0.5 mm in diameter, with a density of distribution roughly estimated at 1 to 2/sq cm. In cat skin, Iggo and Muir [33] noted a density of 4 to 6/sq cm on the inner side of the leg. Limited examination of human skin has revealed no differences in relation to race, age, or sex, although Pinkus [21] speculated that the skin of Orientals and Blacks may have more disks.

Tamponi [36] first noted great variations in the ease with which these structures could be observed in human skin. He was unable to find them in some persons but could find them readily in others. Smith [15] confirmed this, noting that the hair disks were easily observed in the abdominal skin only in two of his eight patients. Tamponi [36] noted that the hair disks were frequent on the neck and absent from the genitals, palms, soles, and face. He also found few hair disks on the volar forearm, as confirmed by Mustakallio and Kiistala [41], but observed them easily on the hairy extensor surface of the forearm. A satisfactory study of these definite regional variations in humans awaits the development of reliable macroscopic techniques of hair disk identification.

A cross section of the tactile disk demonstrates the slight epithelial thickening. The rete ridges of the epidermis are generally effaced at the lower border of the disk, while at its margins there is proliferation, the rete ridges composing an epithelial wall about the structure and setting it apart from the rest of the epidermis. The pigment of the surrounding epidermis is often missing from the hair disk, and provides a light microscopic characteristic of the receptor which separates it from the general epidermis. Winkelmann [8] demonstrated increased pigment in the hair disk of the hairless mouse.

The dermis below the disk is occupied by a heavily myelinated nerve. The myelinated axon

† Cited by T. Kawamura [34].

can supply up to five hair disks in as large an area as 3 sq cm. No other epithelial structure is provided with such a rectilinear, myelinated innervation, which rises frequently without branching from the middle or lower dermis to divide in the papillary dermis immediately below the hair disk into multiple branches, each of which innervates a Merkel cell. Disks have no more than one myelinated axon. Iggo and Muir [33] stated that one disk may contain as many as 50 Merkel cells.

The dermal–epidermal junction is occupied by a group of Merkel cells. The cells are within the epidermis, and the nerve loses its myelin sheath and enters into a close relationship with each Merkel cell as an expanded disk or nerve tissue. Frequently, keratinocyte cytoplasm is observed below the Merkel cell and its innervation. The Merkel cells of the hair disk are identical to the Merkel cells previously described.

HAIR INNERVATION

The vibrissal or sensory hairs of mammals possess intra-epithelial Merkel–nerve complexes. Arnstein (Ostroumow) [42] first demonstrated leaf-like endings in the external root sheath of such hairs by gold and methylene blue methods. Confirmation by silver techniques was provided by Botezat [43, 44], Ksjunin [45], Kadanoff [46], and Winkelmann [8]. Andres [47] stated that these endings represented Merkel's tactile disks, and time has proved Merkel correct.

Patrizi and Munger [48], and Andres [47, 49] have demonstrated the Merkel cell–nerve complex by electron microscopic observation in the upper portion of the sensory hair. They noted that the nerve axon with Schwann-cell cytoplasm investment rests on the basement membrane of the external root sheath. The nerve loses its Schwann-cell covering, becomes intimately apposed to the Merkel cell, and develops an ending with many mitochondria, neurofilaments, myelin figures, and lipid. The Merkel cells are totally surrounded by epithelial cells or neural processes. As described by Patrizi and Munger [48], the Merkel cells are elongated thin cells with a lobulated pale nucleus. These cells contain the typical Merkel granules with their unique polarity for the nerve terminal. "Tonofilaments" and mitochondria are found in the cytoplasm of the Merkel cell. Occasional desmosomes attach the Merkel cell to the adjacent epithelial cells. Andres [47] described finger-like cytoplasmic projections of the Merkel cell in the hair sheath.

The common hair, without a surrounding vascular sinus, has a similar innervation with flattened nerve endings demonstrable among the Schwann cells which are found adjacent to the external root sheath. No Merkel cells have been described within the adult common hair external root sheath [50], despite the expanded flat disks of nerve endings visible by silver methods around such sheaths. Breathnach [23] described Merkel cells in the external root sheath of 16-week fetal human skin. They are numerous at this site but not invariably associated with terminal axons. This type of innervation has not been observed in the adult hair follicle studied by Orfanos [50].

THE HEDERIFORM ENDING OF MERKEL–RANVIER

From the earliest description of the Merkel cell, one pattern of nerve ending with Merkel cells has been repeatedly confirmed by osmium, gold, and silver methods. Ranvier [18] described an ivy-like nerve complex with leaf-like terminations closely applied to the base of the rete ridge of the pig-snout skin. Botezat [6] and more recently Winkelmann [8] noted such nerve ending complexes in the distal glabrous skin. Such complexes are most readily found in the finger skin, but are also observed in toe, plantar, palmar, and nasal skin. In animals with large nasal structures, the principal location may be the nasal epidermis, as in the kangaroo, lemur, opossum, shrew, and other insectivora. Taylor and colleagues [51] described such an ending in the palatal rugae of the hard palate of man.

The basic structure of the hederiform ending is similar to the tactile disk with the exception that no specialized epithelial island is present and the neural-Merkel end-organ is spread along the base of the usual rete ridge. Heavy myelinated A fibers compose the innervation, and two or more fibers arise from the deep dermis to course along the rete ridge in a linear but irregular fashion, dividing into sprays of smaller nerves, each of which bears the silver- or gold-positive, expanded, and flattened nerve mass. About and above each nerve may be found a clear area that represents the Merkel cell. Munger et al [52] described the hederiform ending of Merkel–Ranvier in the skin of the racoon paw, renaming it a "Merkel-rete papilla." It is not easy to see why the rete ridge has been called a papilla—a term commonly reserved for the dermal papilla. Munger et al [52] noted that the Merkel cell here has the typical ultrastructure. Desmosomes attach the cell to keratinocytes. Typical Merkel granules of 100 to 150 nm are observed in the cytoplasm near the nerve ending. No junctional complexes between the Merkel cell and the nerve ending were observed.

THE ORGAN OF EIMER

Eimer [19] described a special intra-epithelial innervation of the nose epidermis of the mole in 1871. Botezat [44] and Winkelmann [8] confirmed this original description. A complete study by Boeke [53] of this neuroepithelial structure indicated that heavy myelinated nerves approach the epidermis, lose their myelin sheath, and divide into 15 to 20 axons which run between the epithelial cells to the stratum granulosum. Boeke [53] believed that a specialized central nerve fiber

was present, that the axons ran through the epidermal cell cytoplasm, that the epidermal cells were modified to act as part of the nerve ending, and that the nerves terminated within the cytoplasm of the epidermal cells. These findings are not supported by the silver and electron microscopic study of this end-organ in the opossum nose, though Munger [54] demonstrated a close relationship between the epidermal cytoplasm and the axon.

At the base of the rete ridge associated with the specialized nasal nerve ending, Merkel cells may be found. These are complexed with the intra-epithelial nerve, so that no definitive statement has been made regarding the relation of the intra-epithelial axons and the Merkel cells. The studies of Halata [55] of Munger [54] revealed that no direct connection was likely; thus, the Merkel cells are terminations in association with special cells, while the intra-epithelial axons terminate freely in little expansions in the stratum granulosum.

Recent publications by Halata [56] and by Suzuki and Kurosumi [57] have given a detailed account of the ultrastructural features of the organ of Eimer of the mole and its innervation. These observations basically agree with those of previous authors but, in addition, draw attention to the occurrence of dermal encapsulated corpuscles associated with nerve terminals proceeding to an overlying organ of Eimer.

DERMAL MERKEL CELLS

Dermal Merkel cells have been described by Breathnach [22, 23] and Breathnach and Robins [30] in fetal human skin. The Merkel cells are most frequently associated with dermal nerve fascicles and mingle with the Schwann cells, which contain the axons (Fig. 5 *A*). Merkel cells have not been observed containing axons in cytoplasmic folds or in a special relation to the Schwann cell. However, free Merkel cells have been observed in the dermis, with limited relationship to any other cell or structure (Fig. 5 *B*). Such cells have been seen only rarely, however, and they may represent cells that are migrating through the fetal dermis to the epidermis. As they approach the epidermis, a basement membrane may unite them with the epidermis or with other nerve structures (Fig. 5 *C*). Only once has a Merkel-type cell been noted in adult skin [32]; such cells must be extremely rare and probably are unimportant, except to indicate that the Merkel cell can exist in this state.

THE GRANDRY CORPUSCLE

Grandry [58] described corpuscles in the subpapillary dermis of the duck and goose bill in 1869. Later descriptions of these end-organs by Dogiel and Willanen [59], Szymonowicz [60], Van de Velde [61], Sfameni [62], and Boeke [53] indicated that this nerve ending consisted of a flattened, expanded nerve disk sandwiched between two "tactile" cells enclosed in small satellite cells and a connective tissue capsule. Myelinated nerves divide to supply a cluster or stack of these neurocellular complexes and, entering the corpuscle, lose their myelin to expand into a neurofibrillar network. Merkel [2] considered the Grandry corpuscle as a "tastzellen"-containing end-organ. Electron microscopic observation of the Grandry corpuscle by de Iraldi [63], Pérez [64], Quilliam [65], and Andersen and Nafstad [66] have indicated that there are actually a central nerve terminal and two supporting "secretory" cells. Andersen and Nafstad [66] specifically refer to the cells of this complex as Merkel cells. Their description and illustrations of the nerve-cell complex in the palate of the hen appears to be compatible with this interpretation. They found large discoid cells with an oval, pale nucleus. The cytoplasmic processes penetrate into the surrounding connective tissue. The cell has a well-developed Golgi region, mitochondria, vesicles, and many glycogen granules. No tonofilaments or desmosomes are observed. The surface of this cell is almost completely covered top and bottom by axoplasm in the shape of a disk. Munger [16] noted also a granular endoplasmic reticulum and dispersed ribosomes. Andersen and Nafstad [66] illustrated a membrane thickening which they believed was a synaptic complex, but their photograph is not convincing. No pinocytosis or clear synaptic vesicles are observed. The laminar cells, which are cholinesterase-positive or associated with the axon, are probably Schwann cells. Although Andersen and Nafstad [66] described dense-cored granules, the number of such granules is not as great as in most Merkel cells. More convincing is Munger's [16] illustration of the granules in Grandry cells. Because the granules appeared to be randomly distributed, Munger did not interpret the cells as being Merkel cells, yet, in all morphologic respects they were comparable, as he recognized and stated.

Saxod [67] described the development of the Grandry corpuscle in the beak of the Peking duck, pointing out that at 20 or 21 days the earliest cells to be observed were already in close relation to unmyelinated dermal nerve. He questioned whether the nerve was the fundamental influence in the development of the Grandry corpuscle. The earliest cells that can be recognized as Merkel cells possess the characteristic dense-cored, membrane-bound granules; however, in the more adult stages, two populations of granules (150 nm and 40 to 100 nm) are found. In the mature cell, Saxod [67] suggested that the Golgi complex forms the specific granules. He clearly showed cytoplasmic protrusions or "horns" of the surface of the Merkel cell. He observed and illustrated synaptic-type vesicles in the nerve terminal, along with neurofilaments and mitochondria. Most important, he clearly demonstrated thick-

ening of the adjacent Merkel and nerve membranes to form synaptic junction and also demonstrated vesicles in relation to this thickening of the Merkel-cell membrane in the skin of a 25-day-old duck embryo.

PHYSIOLOGIC RESPONSE AND FUNCTION

The classic paper by Iggo and Muir [33] indicated the physiologic response of the tactile disk with its Merkel cells and myelinated innervation in the cat skin. They noted by means of single-fiber recording that this receptor produced slowly adapting high-frequency discharge. They labeled this the type I slowly adapting receptor of haired skin to distinguish it from the type II slowly adapting receptors of haired skin which were unassociated with hair follicles or tactile disks. This separation of type I from type II receptors has been confirmed by Tapper [68] and Burgess et al [69]. The tactile disk gives minimal or no response to any stimulus except a mechanical one and the response is highly localized. Motion of an adjacent hair of the adjacent skin does not produce a response. Mechanical stimulation of the dermal side of the tactile disk through a slit in the epidermis by its side produces no response. Only a few of the corpuscles have a resting discharge in the absence of an applied stimulus. The mean frequency of such a discharge is always low, and the interspike interval is characteristically irregular, in contrast to the type II slowly adapting ending.

It was found that the dynamic response of the tactile disk could be separated into two components: one dependent on the velocity of the indentation and the other dependent on the amount of indentation.

The response of the corpuscle generated impulses at more than 1,000/sec, and this frequency of the nerve response was directly dependent on the velocity and amplitude of the mechanical displacement. The sustained response to mechanical deformation continued for 30 minutes.

The touch corpuscle can provide excellent localization of a mechanical alteration of the skin. The mean number of corpuscles of cat skin supplied by 100 axons of the saphenous nerve was

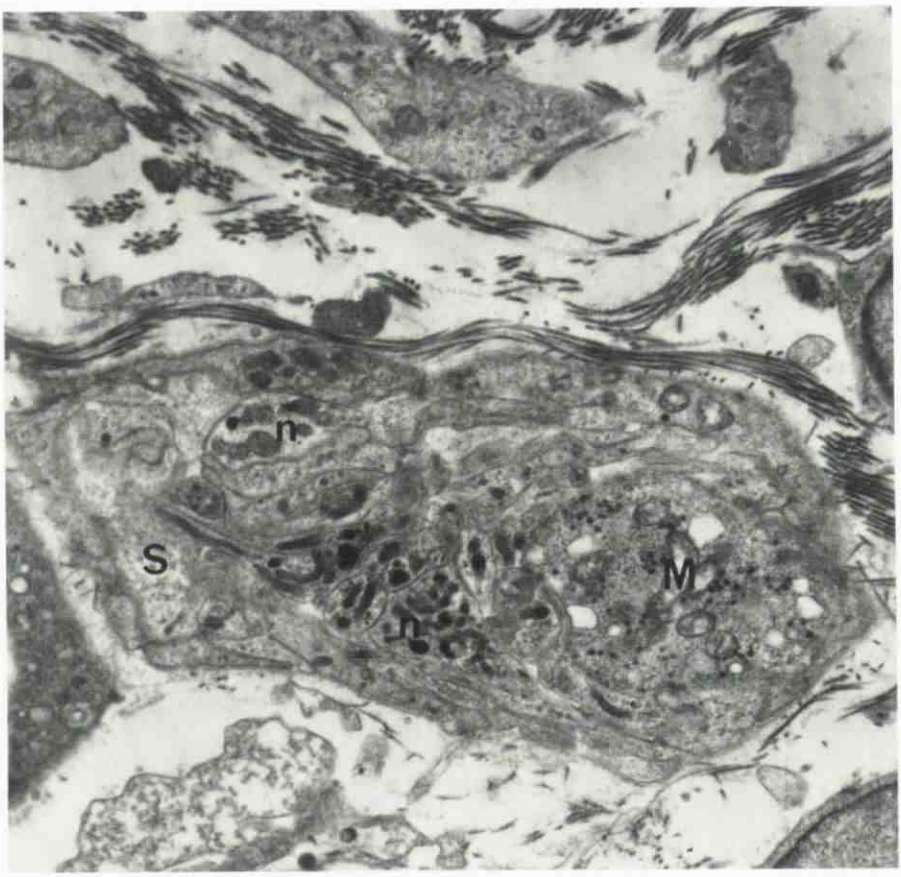

FIG. 5. *A*. Merkel-Schwann complex from dermis of finger of human fetus. *M*, Merkel cell with cytoplasmic granules; *S*, Schwann-cell cytoplasm; *n*, neuraxons. (× 8,160.) (From Breathnach AS: Embryology of human skin: a review of ultrastructural studies. J Invest Dermatol 57:133, 1971. By permission of The Williams & Wilkins Company.)

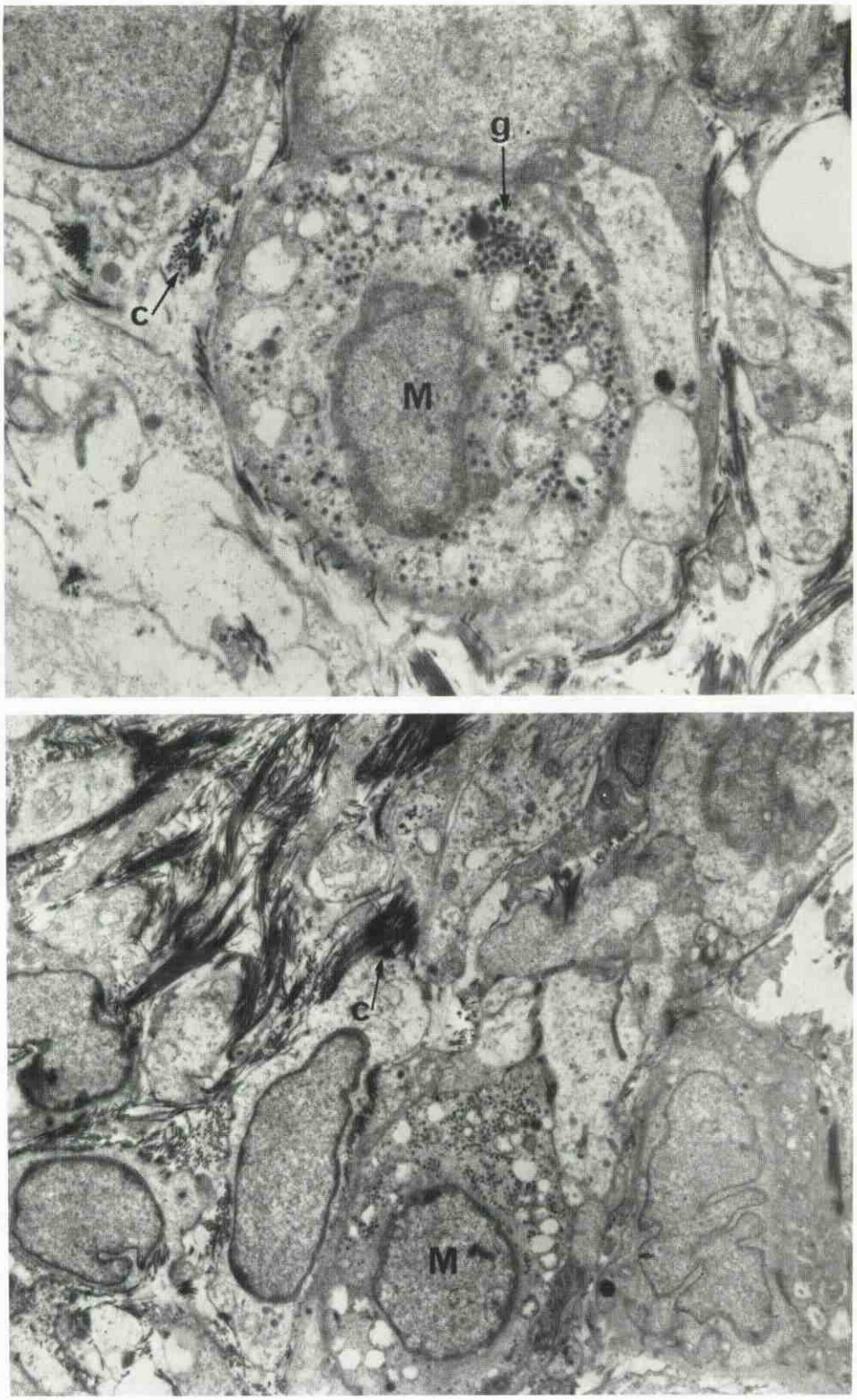

FIG. 5. *B* (top). Merkel cell (*M*) lying free among other cells and collagen fibers (*c*) in dermis of finger tip of human fetus; *g*, granules. *C* (bottom). Merkel cell (*M*) lying free among other cells and collagen fibers (*c*) in dermis in finger tip of human fetus. (× 5,100.)

1.84/axon. Only tactile disks cause responses in the related nerves. Because the tactile disk is functional in newborn cat skin, before Merkel cells are present, as studied by the PAS method, Kasprzak et al [17] proposed that the terminal branches of the type I afferent nerves were the transducers. This proposal must be studied by electron microscopy.

The touch corpuscle can be excited by a decrease in temperature of the skin. An increase in the rate of discharge also occurs when the temperature is lowered. Iggo and Muir [33] noted that the response could be confused with a similar one from cold receptors.

The tactile disk in cat skin is fully functional at birth, but the velocity of conduction only reaches 25 m/sec at 49 days. Burgess et al [69] noted that type I fiber conduction velocity was 54 to 72 m/sec in the adult cat. Brown and Franz [70] found, by studying isolated axons of the adult rabbit sural nerve, that the axons with the fastest conduction velocities (more than 70 m/sec) and the lowest threshold to electric stimulation were exclusively associated with type I slowly adapting units or tactile disks.

Tapper [68] demonstrated in conditioned cats that a small mechanical stimulus of a single tactile pad of the hairy skin can evoke a behavioral response. Responses could be obtained with a stimulus that was ineffective in surrounding skin. He deduced that the tactile hair disk was selectively sensitive or that, by its central connections, it was a more potent behavioral activator. Tapper and Mann [71] also demonstrated synapses in the dorsal spinal gray matter, but section of the dorsal spinal funiculus did not change the selective sensitivity. The specific spinal paths are unclear, but Brown and Franz [70] stated that the spinocervical tract was not involved. Iggo and Ramsey [72] utilized the evoked potential technique to demonstrate that such endings in the skin could be recorded a few millimeters rostral to the longitudinal sulcus in the contralateral cortex and 4 mm lateral to the midline.

Mustakallio and Kiistala [41] proposed that the Merkel cell was a potential monoamine storing cell of the human epidermis, the proposal being based on the structural similarity of the granules to monoamine-storing granules. Iggo and Muir [33] treated cats with 1 mg of reserpine intramuscularly for 4 days, enough to abolish transmission to the nictitating membrane after cervical sympathetic stimulation. The function of the corpuscle was unaffected by this treatment, and no ultrastructural change in the cells was observed. Kurosumi and Suzuki [73] recently stated that considerable degranulation of Merkel cells occurred after reserpine injection. Studies by Fjällbrant and Iggo [74] have shown that histamine, serotonin, and acetylcholine have an initial stimulating and later depressing effect on type I slowly adapting receptors. Smith and Creech [75] recorded action potentials in axons from tactile hair disks and found that nicotine, lobeline, veratrum, potassium, calcium, and magnesium blocked the response of the epidermal receptor. Acetylcholine, serotonin, and catecholamines had no effect. They concluded that none of the usual neurotransmitters were involved in activity of this receptor. Kurosumi and Suzuki [73] noted that Merkel cells degenerated when the sciatic nerve was cut, a finding that must be confirmed and extended.

DISCUSSION

The distinctive features of the Merkel cell may now be contrasted with those of the other intra-epithelial nonkeratinocytes. The Merkel cell is usually an intra-epithelial cell with a light, organelle-rich cytoplasm and a deeply folded nucleus. Both of these features are found in the intra-epithelial Langerhans cell, but the cytoplasm of the Langerhans cell contains the unique Langerhans granule with internal periodicity of 9 nm and does not develop desmosomes or the characteristic Merkel-cell granule. The Langerhans cell in many species contains nucleoside triphosphatase or other hydrolytic enzymes which permit its identification by light microscopy; to date no histochemical enzyme methods have yielded positive reactions with the Merkel cell. Ultrastructural localization of nucleoside triphosphatase within the Langerhans cell in guinea-pig skin and in human skin grown in tissue culture has confirmed the specificity of this reaction. Similar electron histochemical studies of the Merkel cell probably will be negative. No relation to nerve has been demonstrated for the Langerhans cell. The Langerhans granule has not been observed in the Merkel cell or in adjacent nerve cells or tissue.

The Merkel cell can likewise be distinguished ultrastructurally from the basal epidermal melanocyte. The melanocyte contains individual melanosomes at different stages of maturity, but not the characteristic Merkel granule. Merkel cells may contain melanosomes, but they are invariably mature and in groups within a membrane-bound organelle (compound melanosome); this indicates that the melanosomes are not synthesized within the cell but are of extraneous origin. No melanocyte possesses the rudimentary desmosomes observed in the Merkel cell, and no melanocyte in the epidermis possesses the nerve terminal association observed with the Merkel cell.

The polymorphonuclear leukocyte and the lymphocyte can invade the normal epidermis and are frequent in gingiva. These cells are observed in the intercellular canals and have no fixed relationship with the epithelial cells. They do not possess the cytoplasmic granule or the neural association of the Merkel cell. The mast cell which is frequently found in the peripheral nerve trunks contains a unique granule and is occasionally ob-

served in the epidermis although probably not in normal conditions. The mast-cell granules are much larger than Merkel granules and of different morphology, being granular, laminar, or whorled. The Merkel-cell granule is distinctively different and is not observed in the mast cell.

The presence of desmosomal attachments between the Merkel cell and the adjacent epithelial cells has initiated the concept of an epithelial origin for the Merkel cell. The desmosomes observed are small, poorly developed, and few in number. Little or no cytoplasmic fibrillar attachment to the desmosomes is noted. This finding is reminiscent of the simple desmosomal attachments observed between Paget's cells and epithelial cells. Specialized contacts can develop between contiguous but dissimilar cells in various tissues, and we do not believe the presence of desmosomes per se establishes the epithelial origin of the Merkel cell. The lack of development of tonofilaments, keratinosomes, keratohyalin, or any of the structural equivalents of the cytoplasmic contents of the normal, progressively keratinizing keratinocyte supports this view. No Merkel granules have been observed in keratinocytes. Because of the absence of keratinization and of the absence of transitional cell forms, we do not find the theory of epidermal origin of the Merkel cell satisfactory. Besides, the embryologic evidence cited previously is totally against this view.

If the distinctive Merkel cell is not ontogenetically related to the Langerhans cell, the melanocyte, the leukocyte, the mast cell, or the epidermal keratinocyte, it may be considered as representing a unique cell line. This view is based on its unique structural characteristics, on the absence of transitional cells during development, and on its continued relationship to nerve tissue. The Merkel cell is associated with dermal and epidermal nerves but is unlike any other sensory cell in the central or peripheral nervous system. It is easily distinguished from the Schwann cell, which also has a close relationship to myelinated and unmyelinated nerve fibers but which has no specific cytoplasmic granules and possesses a basement membrane about it. It most closely resembles cells of the sympathetic ganglion, which possess larger, dense-cored granules that contain catecholamines. Such granules have a definite relationship to the cell membrane and to synaptosomes, and the catecholamine content is depleted by reserpine. The only relation to cell membrane of the Merkel-cell granule has been observed in the very specialized cells of the corpuscle of Grandry. These cells also contain other unique granular and laminated organelles of unknown nature. The Merkel-cell granules of the cat tactile disk are unchanged by reserpine treatment, and no evidence of their catecholamine nature exists at the present moment. We cannot, therefore, equate this cell with the sympathetic catecholamine-containing cells of the nervous system, but because we consider this cell a member of a functioning sensory unit, we cannot entirely forget the comparable appearance of such cells.

The Merkel cell is associated with nerve fibers in the epidermis and dermis. As seen by light microscopy and neurophysiologic studies, these are fast-conducting, myelinated, A fibers, usually equated with touch sensation. Since the study of Iggo and Muir [33], it is considered that a specific type of epithelial-Merkel-nerve cell receptor complex is formed in the tactile disk, which gives a slowly adapting, characteristic discharge on physical stimulation. This receptor complex may take many forms as outlined in the Table. It confers a low threshold for mechanical stimuli on the epidermis and by analogy must increase the sensory response of the epithelial and dermal tissue in which it may be found.

The Merkel cell joins the other cell symbionts of the epidermis, the melanocyte and the Langerhans cell, as an additional unique nonkeratinocyte capable of migration from the dermis to the epidermis. It joins the melanocyte as an additional cutaneous cell of probable neural-crest origin. It joins the mammalian end-organ as a unique, slowly adapting, cutaneous, touch receptor. Because it is a distinctive cell type, we may eventually find some aberrent proliferation or tumor of Merkel cells, just as a probable tumor of Langerhans cells has been found in histiocytosis X. Before this occurs, however, many fundamental embryologic, denervation, physiologic, and biochemical studies remain to be done.

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