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MELANOMA STUDIES *

III. A THEORY OF PIGMENTED MOLES. THEIR RELATION TO THE EVOLUTION OF HAIR FOLLICLES

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CONTENTS

I. THE PIGMENTED MOLE AS A TACTILE TUMOR

Discussion of the origin of pigmented moles should begin with a mutual understanding of just what a pigmented mole is. All readers will agree, we believe, that the pigmented mole is an abnormal growth in human skin, that it is pigmented, usually elevated, often hairy, and that on microscopic examination groups of nevus cells are found in the corium. We shall make the further claim that the pigmented mole shows distinct traces of having been at one time a tactile organ with a full complement of sensory nerves and tactile terminals. It is at this point that differences of opinion arise. It is at this point therefore that we shall begin to present our evidence.

Nerve Terminals in Moles

Any good neural silver stain applied to a pigmented mole will reveal branching nerve trunks, as pictured in Figure 1. There is

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nothing unusual about a nerve trunk branching in human skin. All normal skin offers these pictures. We would direct attention to the smaller branch which leaves the crotch of the main trunk and passes to the right. This nerve divides and subdivides into fine threads. The threads terminate in tiny bulbs in contact with some of the nevus cells which form the background of the picture. This is exactly the manner in which many nerves terminate among the Merkel-Ranvier tactile cells of the hair follicles and the basal cells of the epidermis. Such a distribution of nerve fibers is never found in normal human corium but it is a common sight in pigmented moles.

Figure 2 shows a more elaborate distribution of nerves in another mole. The background is a solid sheet of nevus cells among which the nerve fibers ramify, the fine threads winding around the nevus cells and terminating as tiny end-bulbs in intimate contact with some of them.

Figure 3 shows another neural distribution which is common in hairy moles. The most prominent feature of the picture is the hair in its follicle. At the left of the follicle a nerve divides. Some of the branches pass upward and to the right to supply the follicle. These nerves terminate in tiny end-bulbs in contact with epithelial cells of the follicle, which consequently are regarded as cells specialized for the reception of tactile impulses. Other branches diverge upward to the left and downward to the right. These branches terminate in end-bulbs on and among the nevus cells. If the epithelia of the hair follicle are accepted as specialized tactile cells by virtue of their innervation it is a fair proposition that the nevus cells also are tactile cells by virtue of an exactly similar innervation. Pictures of such joint innervation of hair follicles and nevus cells might be multiplied indefinitely.

The tactile nature of these neval nerves was demonstrated in another way by Masson (1926, 1931, 1932),[1, 2, 3] as shown in Figure 4, a Masson-Mallory trichrome stain of a paraffin section of a mole from the occiput. The section is from Professor Stout's collection. Like many moles on or near the scalp, this one is crowded with figures which Masson first described and, we believe, interpreted rightly as caricatures of meissnerian tactile corpuscles. Masson's demonstration of tactile corpuscles in pigmented moles has been corroborated by Stout (1932),[4] Ewing (1928, 1930),[5, 6] Foot (1931),[7] who presented convincing preparations at the meeting of the American Association of Pathologists and Bacteriologists in Philadelphia last year, and by Frantz and McFarland (personal communications).

Figure 5 shows another common sight in pigmented moles when stained for nerve fibers. It is what we call the cable effect. Around a few neurites traversing the colorless corium there is an enormously thick sheath of cells. Such pictures are characteristic of von Recklinghausen's neurofibroma of the skin; in fact, it was this formation that led Soldân (1899)[8] to declare unequivocally that the pigmented mole is a neurofibroma. Using Weigert's myelin stain Soldân demonstrated medullated fibers only; he did not use silver.

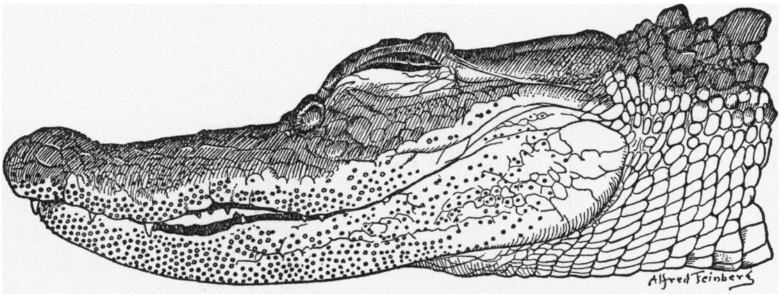
Figure 6 is a normal meissnerian corpuscle from the sole of the human foot. It is introduced for two purposes, to show that our staining technique is actually specific for nerve fibers and to demonstrate that, with this technique at least, the nerves are seen to terminate among the well recognized tactile cells of the meissnerian corpuscle exactly as they do among the nevus cells.

Assuming that we have come to an agreement that pigmented moles contain sensory nerve fibers and cells that appear to be tactile cells because of their neural contacts, together with structures resembling meissnerian tactile corpuscles, let us pass to a consideration of their possible origin. For all tumors or for almost all tumors, there is a prototype, that is, some adult or embryonic tissue of which the tumor is a more or less faithful reproduction. It is a striking feature of pigmented moles that they do not resemble anything known in normal mammalian skin. No normal mammalian corium contains groups of cells, innervated, pigmented and elevated in the manner characteristic of pigmented moles. If, however, we look at the creatures just below the mammals in the phylogenetic scale, the reptiles and the amphibia, we shall find them peppered with pigmented dots which on microscopic examination present the structure of human pigmented moles.

II. The Reptilian Tactile Spot

Text-figure 1 represents the head of the common alligator. Along the upper and lower jaws there are many black dots standing out prominently on the smooth, white skin. Each dot is a sensory nerve terminal, generally accepted by zoölogists as a tactile organ. Such tactile organs are common to reptiles and amphibia. They were discovered in the frog by Merkel (1880)[9] and called by him *Tastflecke*, tactile spots.

Figure 7 is a vertical section through one of these tactile spots stained for nerve fibers. You will note that the tactile spot is elevated and pigmented, and that there is a group of cells in the corium just beneath the epidermis. These are Merkel-Ranvier tactile cells mixed with Schwann cells from the nerve fibers. The ascending nerve breaks into fine terminal threads which wander among the tactile cells just as similar terminal threads wander among the nevus cells. Some of the threads terminate as end-bulbs, some as menisci, in contact with a tactile cell; some continue on into the epidermis. You will recognize the resemblance of this structure to that of the



TEXT-FIG. 1. Alligator Missisippiensis

innervated pigmented mole. There is the same elevation, the local accumulation of pigment, the group of tactile cells in the corium and the fine nerve fibers winding among the tactile cells, terminating on some of them as end-bulbs and menisci.

Figure 8 is a tactile spot from the palate of the alligator. There is no pigment to confuse the picture and you may have a clearer view of the group of tactile cells in the corium, separated from the epidermis by a narrow strip of corium, and the nerve fibers terminating on and among the tactile cells.

Good illustrations of the microscopic appearance of tactile spots may be seen in the reports of Merkel (1880)[9] and Hulanicka (1909, 1913).[10, 11] Pinkus (1927, p. 346)[12] reproduces one of Hulanicka's drawings of a tactile spot of the alligator's tongue, which bears a striking resemblance to the microscopic picture of a pigmented mole.

The question now arises — What possible connection can there be between pigmented moles of human skin and these pigmented reptilian spots that resemble them so closely? The answer is to be found in the evolution of the hair follicle.

III. The Evolution of the Mammalian Hair Follicle

In the course of evolution, as the mammal evolved from a reptilian form, the reptilian tactile spots disappeared. As tactile organs they were replaced by hair follicles, which appeared first in mammalian skin.* If we can picture to ourselves a point on mammalian skin where this transformation has not taken place completely, a point where hair follicles have appeared but where reptilian tactile spots have not disappeared, we should have a fair picture of a pigmented, hairy mole. Insert a few hairs in the tactile spots of this alligator and again you would have a good likeness of a hairy, pigmented mole.

The pigmented, hairy mole, then, appears to be a link or transition from pigmented tactile organs of the amphibian-reptilian type to hairy tactile organs of the mammalian type. It offers a picture that is only partly mammalian, the other part being reptilian. In its hair follicles it is mammalian; in its pigmentation, elevation and in the groups of innervated tactile cells in the corium it follows the amphibian-reptilian pattern.

We are well aware of the obscurity that veils the early steps of the evolution of mammalian hair. Animals intermediate between reptile and mammal have largely disappeared or are known only as fossils, of little use in the study of nerve terminals. We are familiar also with the hypotheses by which Maurer (1892, 1895, 1922),[15, 16, 17] Oppenheimer (1896),[18] Botezat (1914),[14] Broman (1920, 1921),[19, 20] Preiss (1922),[21] Plate (1922)[22] and others have sought to bridge this evolutionary gap. Discussions and bibliographies may be found in Botezat (1914),[14] Pinkus (1927)[12] and de Meijere (1931).[23] Among these varied and often conflicting opinions the chief supports of our hypothesis stand unshaken. Everyone agrees that the skin of modern reptiles and amphibia contains innumerable tactile spots and that in some manner mammalian skin has succeeded in replacing the reptilian tactile spots with mammalian hair.

* Zoölogists hold that hair is primarily a tactile organ, adapted secondarily to the functions of color and bodily warmth (Plate, 1922, p. 308,[13] Botezat, 1914, p. 25, 27, 31 [14]).

Der Spitzmaus

The possibility of the persistence in mammalian skin of nerve terminals resembling amphibian tactile spots needs no lengthy argument, for it actually occurs in one of the shrews. Merkel himself, discoverer of the tactile spot, writes that among the hair follicles on the back of the Spitzmaus (*Sorex pygmaeus*) he saw "nerve fibers ending in groups of cells which lay just beneath the epidermis. These are certainly end-organs but they looked much more like amphibian tactile spots than the customary tactile corpuscles of mammals" (1880, p. 143).[9]

IV. The Pigmented Mole as a Phylogenetic Tumor

The more imaginative of the medical profession have long held a vague belief in the existence of phylogenetic tumors (Bland-Sutton, 1893, p. 493),[24] and among phylogenetic tumors they have been especially impressed by the resemblance of hairy moles to the skin of the lower mammals. Pathologists generally had accepted Cohnheim's teaching (1877)[25] of the origin of certain tumors in groups of cells that had remained unutilized in the building of the human embryo, when Ribbert (1906)[26] pushed some origins farther back and declared that uterine adenomyoma, intestinal polyposis and pigmented moles could not be explained as aberrations in the growth of the human embryo, but that they were easily intelligible as imperfect survivals of structures normal to animals lower in the phylogenetic scale. Mathias (1920, 1922)[27, 28] came to the same conclusion concerning tumors arising in aberrant pancreas and parotid tissue, noting that such scattered distribution of these glands is normal in earlier evolutionary forms. He proposed grouping such tumors under the name progonoblastoma (*progonoi*, ancestors), and Jendralski (1921)[29] described a pigmented mole of the conjunctiva as a progonoblastoma.*

Meirowsky (1926)[30] wrote of congenital vitiligo and pigmentation: "Since they correspond so closely with the markings of the lower animals, it follows that in human skin there exist phylogenetically fixed localizations in which a change to nevus formation can occur."

* Mathias (1922)[28] announced a forthcoming publication to be entitled: "Zur Auffassung der Naevi als Atavismen im Sinne der Progonoblastom." This paper was never published (personal letter).

Searching in human skin for some vestige of the tactile hairs (sinus hairs) which are widespread among mammals other than man, Henneberg (1915)[31] thought to find them in pigmented, hairy moles, a view advanced also by Friedenthal (1908),[32] by Sklarz (1926),[33] and by Sulc (1926),[34] who includes vascular nevi as vestiges of the blood sinuses of sinus hairs. In this group of phylogenetic tumors, Šikl (1932)[35] inclines to place two benign epitheliomas of human skin containing mucus-secreting goblet cells, a common feature of the skin of the lower vertebrates but known among mammals only in the skin of the hippopotamus; and Kyrle (1925, p. 253)[36] regards human syringocystadenoma as a vestige of the apocrine glands of the lower mammals.

The ideas of this period were well summarized by Maurer (1929) [37]: "A man is not merely the child of his parents. He is rather the end-product of an immeasurable line of ancestors whose witnesses are the single steps of his embryonic evolution and the many vestiges in his finished form. Such testimony shows that the genes of the impregnated ovum contain the hereditary factors of many different types of animals." *

Back to the Reptile

In explaining the origin of pigmented moles on the principle of phylogenetic atavism all writers without exception have made the same blunder. They forget the nevus cells. From Ribbert onward, they have compared moles in a general way to "the pigmented skin of the lower animals," or more specifically to the hairy tubercles of mammals other than man. But there are no nevus cells in the pigmented skin of the lower mammals or even in their hairy tubercles, whereas nevus cells are an almost constant feature of pigmented moles. Moreover these writers overlooked the nerve fibers. Since the work of Soldán, and especially of Masson, we can no longer hold the simple view that pigmented moles are mere bits of brown or hairy skin inherited from remote mammalian ancestors. When Masson showed that pigmented moles are tumors of the sensory nerves of the skin, that some of the nerves terminate on the nevus

* The phylogenetic sequence of pigmented, hairy moles may be viewed in reverse, making the mole itself the starting point of anthropological studies and working backward, as Samberger (1933)[38] has done with naevus acanthosiformis.

cells, and that some pigmented moles contain myriads of meissnerian tactile corpuscles, he obliged the palingeneticist to shift his ground from the study of remote ancestors with pigmented, hairy skins to the study of remote ancestors with pigmented tactile terminals buried in the corium. In so doing we must pass over the entire series of mammals, where no such terminals exist (the end-organs of Merkel's shrew are neither pigmented nor elevated), to ancestors still more remote, the reptiles and amphibia, where pigmented tactile terminals buried in the corium abound. Here at last in the reptilian tactile spot we find a full length portrait of the human pigmented mole, a pigmented elevation of the skin and a nerve coming up from below to innervate a group of tactile cells in the corium.

A phylogenetic theory of pigmented moles must give nerve fibers and nevus cells equal rank with hair and pigmentation. It is true that hair, pigmentation and nerve fibers might represent merely the reappearance in human skin of a patch of mammalian hair, but the innervated nevus cells inexorably carry us farther back, linking that mammalian hair with its evolutionary predecessor, the reptilian tactile spot.

V. Ontogenesis

Whether or not we accept a phylogenetic influence in the formation of the pigmented, hairy mole in human skin, we must still seek the immediate fault in the skin of the individual possessing the mole, in ontogenesis. In this search the reptilian aspect of the pigmented mole may prove to be a useful guide. Since the mole is overwhelmingly congenital and often hereditary its ground must have been laid during embryonic life. There is then a certain point in the growth of human embryonic skin when the dipping epidermis and the advancing nerve fibers, which normally coöperate to construct innervated hair follicles, revert to the construction of innervated reptilian tactile organs. One would be inclined to seek this point in a stage of the human embryo when it has not yet diverged greatly from the form and potencies of the reptilian embryo.

Experimental embryology is showing that the various tissues, and in some cases organs, which develop harmoniously to form the individual, are determined very early in embryonic life (Lillie, 1929).[39] That is to say, an irreversible change occurs in the nature of the still undifferentiated part which restricts its future capacity for development. By such a restrictive change, for example, the cells composing the primitive ectoderm are segregated into those capable of developing into neural tissue and those whose potency is restricted to the production of epidermis. Parts of the epidermis in their turn are progressively restricted to the production of lens, and so on, and finally hair, feathers and other late appearing structures. There are relatively few kinds of such segregates, and the number varies but little throughout the whole vertebrate series.

In the ontogenetic development of the mammal, as compared with that of the reptile, hair appears as a new segregate and simultaneously the tactile spot is lost. If these two organs could be conceived of as segregates from a predecessor equipotential for both, hair being induced by conditions normal to the developing mammalian skin and the tactile spot by conditions normal to the developing reptile, the appearance of the congenital pigmented mole in mammalian skin might be postulated as due to some slight local variation in environment at a critical period. Such a local variation might be of circulatory or neural origin.

The Vascular Nevus

The phylogenetic hypothesis might be extended to vascular nevi. The most primitive amphibia had no lungs; they breathed entirely through the skin. Many salamanders living today have preserved this primitive type of respiration, bearing in their skins a rich capillary plexus that serves as a cutaneous lung. The capillary plexus of vascular nevi may be interpreted as a vestige of the respiratory plexus inherited from that far-off ancestor, the primitive amphibian that breathed through the skin.

Summary

Photomicrographs of silver-stained sections are presented to show that pigmented moles are rich in nerve fibers and tactile cells. End-bulbs of nerve fibers make contact with nevus cells exactly as they do with the tactile cells of the epidermis and of the hair follicles.

Masson's observation of a profusion of structures resembling meissnerian tactile corpuscles in certain pigmented moles is confirmed.

In its elevation, pigmentation, innervation and the groups of tactile cells in the corium, the pigmented mole bears a striking resemblance to the tactile spots of reptiles and amphibia.

In the course of evolution the reptilian tactile spots were replaced by mammalian hair follicles. The pigmented, hairy mole appears to be a link or transition from pigmented tactile organs of the reptilian type to hairy tactile organs of the mammalian type. In its hair follicles it is mammalian, in its pigmentation, elevation and in the groups of innervated tactile cells in the corium it follows the amphibian-reptilian pattern.

Phylogenetic and ontogenetic hypotheses are presented.

For helpful criticism and advice on zoölogical questions and for reptilian material we are indebted to Dr. G. Kingsley Noble of the American Museum of Natural History, to Drs. H. E. Anthony and George G. Goodwin of the same Museum, and to Dr. W. J. Hamilton, Jr., of Cornell University for specimens of American shrews. Dr. Jerome Webster has long taken a friendly interest in these studies, contributing many pigmented moles from his clinic of plastic surgery. To Professor Purdy Stout, the most generous and self-effacing of laboratory directors, we owe many valuable suggestions and choice material.

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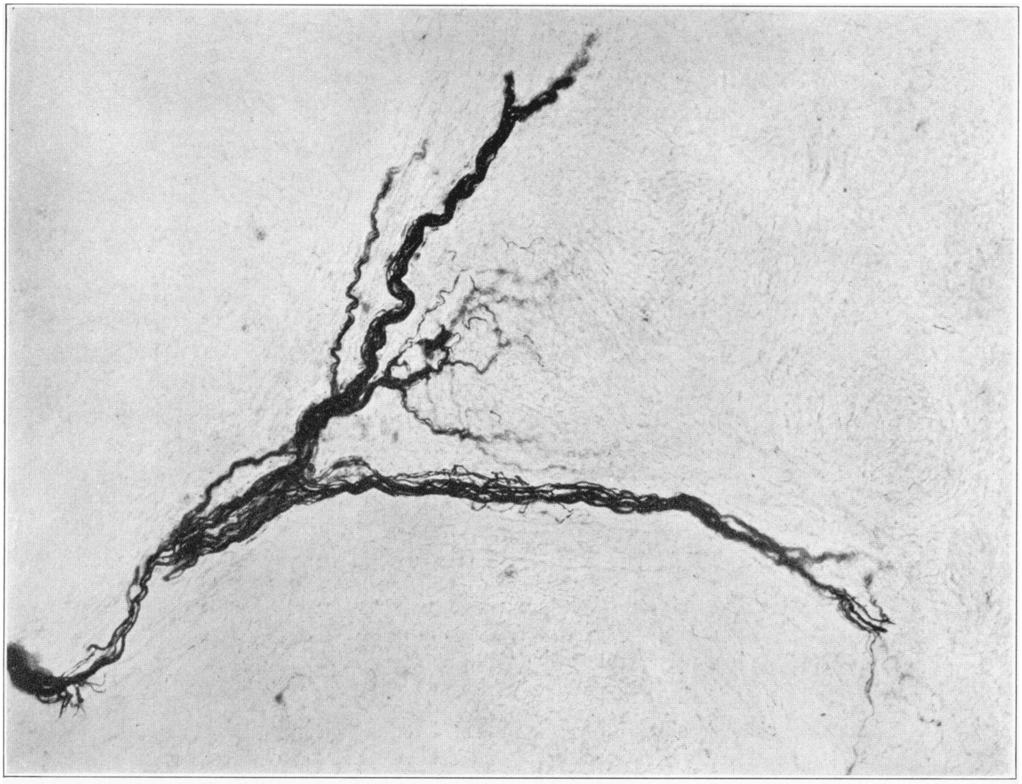
DESCRIPTION OF PLATES

With the exception of the paraffin section of Figure 4, all tissue was fixed in formalin slightly alkalinized with sodium hydrate or pyridin. Thick frozen sections were stained by Laidlaw's 2 minute silver technique for neurites. This is a modification of Gros-Bielschowsky. Gold toning was omitted. With this technique collagen is usually colorless, cytoplasm colorless to pale yellow, nuclei yellow to brown, and neurites black. The sections are cut very thick, 50 to 75 microns, in order to follow the course of the nerves for long distances. With these black neurites on a colorless or pale yellow ground thickness of the section is no obstacle to satisfactory microscopic examination, although thick sections are not so suitable for photography. Photomicrographs were taken through Wratten filters.

PLATE 133

FIG 1. A nerve trunk branching in the center of a very cellular pigmented mole. The ground is a broad sheet of nevus cells, pale yellow in the section but scarcely distinguishable in the photograph. Just above the crotch of the nerve a short branch goes to the right, soon breaking into fine threads that wind among the nevus cells and end on some of them as tiny bulbs. This is the characteristic termination on tactile cells.

FIG. 2. Distribution of a nerve in a pigmented mole. The entire background is a broad sheet of nevus cells, seen indistinctly in the picture. At the left a nerve trunk gives off many delicate threads that wander among the nevus cells and end as tiny bulbs on some of them. The black figures on the extreme right are short sections of nerve trunks.



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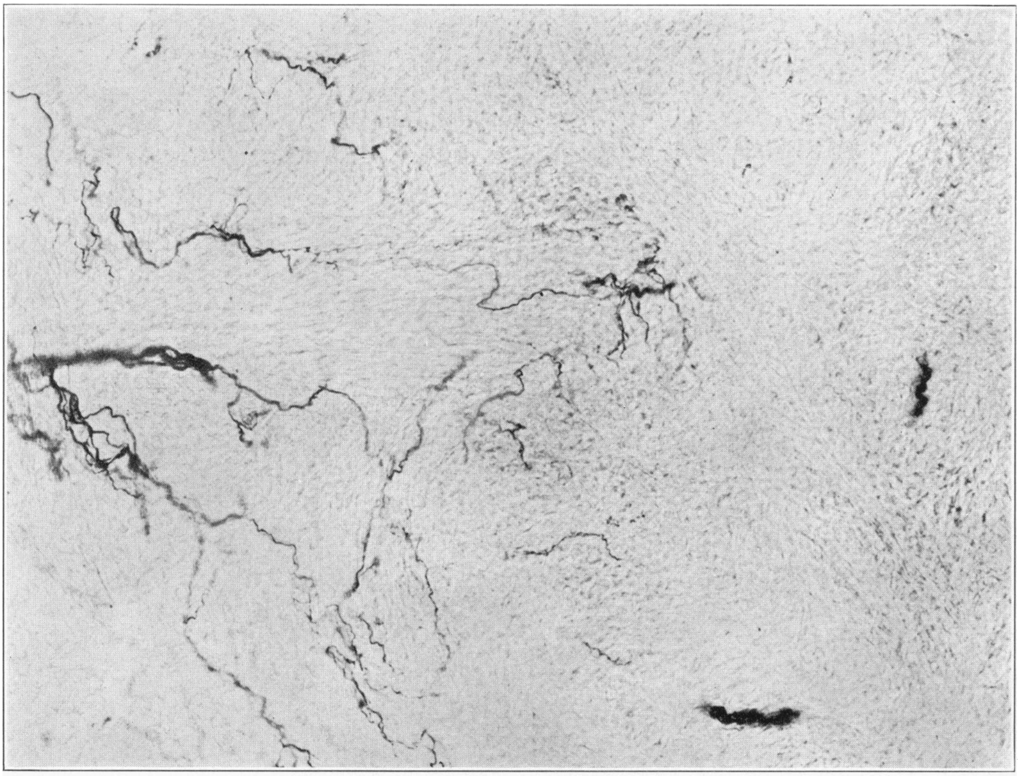

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PLATE 134

FIG. 3. Joint distribution of a nerve to a hair follicle and to the surrounding nevus cells. In the right upper corner is a hair in its follicle. The epithelium of the sheath is invisible, colorless in the section. The rest of the picture is a broad sheet of nevus cells. In the center a cross-section of a nerve trunk is seen just at the point where it is dividing. Some branches pass upward and to the right to supply the sheath of the hair follicle. These branches end as tiny bulbs among the epithelia of the hair follicle. Other branches pass upward to the left and downward to the right among the nevus cells. These branches end as tiny bulbs on the nevus cells exactly as the other branches end on the tactile epithelia of the hair follicle. Such joint innervation of hair follicles and nevus cells is very frequent.

FIG. 4. Paraffin section of a pigmented mole from the occiput, fixed in Bouin's fluid. Masson-Mallory trichrome stain. Instead of the usual groups of nevus cells this mole consists almost entirely of round and oval figures, laminated and nucleated, closely resembling meissnerian tactile corpuscles.

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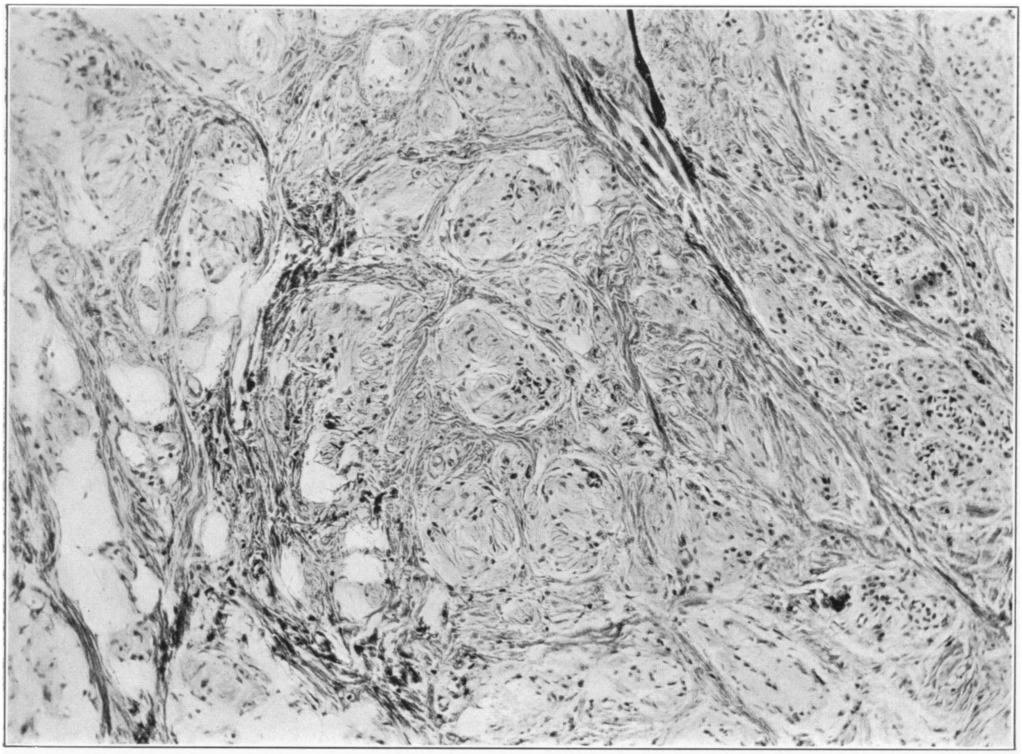

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PLATE 135

FIG. 5. From the margin of a pigmented mole. The dark band across the top is epidermis, moderately pigmented but unduly blackened by the silver. Well below the epidermis, running across the colorless corium, is a slender bundle of black neurites, cut by the knife into three sections. The neurites are enclosed in a very thick sheath of cells that blend with the surrounding corium without sharp demarcation. There is no limiting perineurium. This formation is characteristic of neurofibroma of the skin.

FIG. 6. Nerve skein of normal meissnerian corpuscle from the sole of a human foot. The corpuscle lies in a broad, colorless papilla. The irregular black band above it and to the left is normal epidermis. Of the nuclei of the corpuscle, only a few are stained. The nerve skein of the corpuscle is broken into three sections, as often seen in these long corpuscles. The neurites end as bulbs of various sizes in contact with the tactile cells of the corpuscle. In some corpuscles the end-bulbs are enormous. Just below these corpuscles lateral branches often leave the nerve to supply the adjoining epidermis.

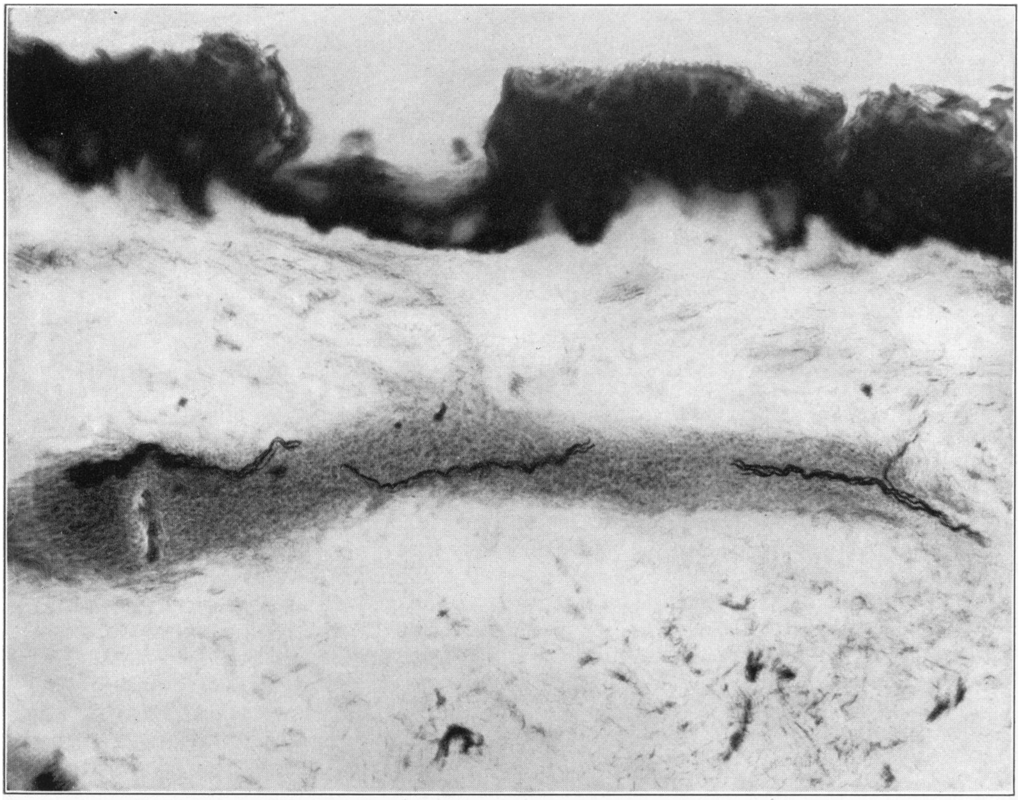

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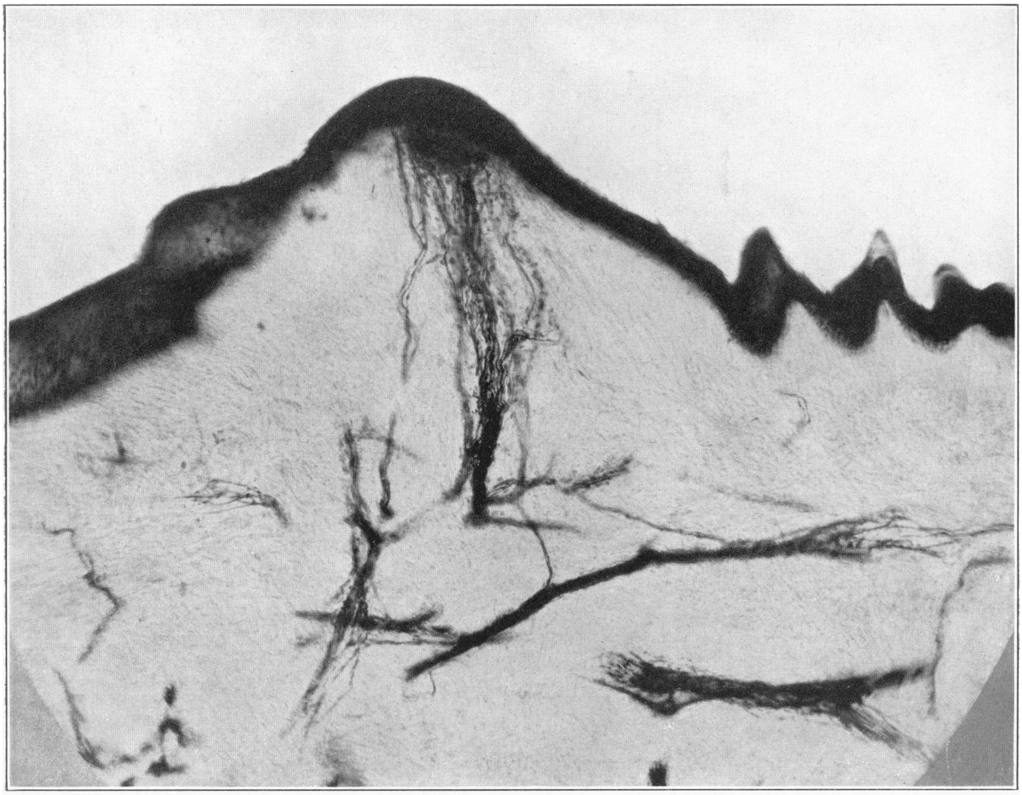
Plate 136

Fig. 7. Vertical section through the black tactile spot of an alligator's jaw. Note the conical elevation of the derma with its group of tactile cells. In the natural state the pigmentation is limited to the elevation; in the picture the whole epidermis has blackened in the silver. The black figures in the lower and middle areas are nerve trunks from which many branches ascend to supply the tactile spot. Here they break into fine threads that wind among the tactile cells and end as tiny bulbs or menisci on some of them. The group of tactile cells constituting the spot lies just beneath the epidermis. Between the tactile cells and the epidermis there is a narrow strip of corium which does not show in the picture, the section being very thick. Some nerve fibers continue upward across this strip and enter the epidermis. According to Plate (1924, pages 61 and 63), the meissnerian corpuscle of human skin is a direct evolutionary form of these reptilian tactile spots.

Fig. 8. Tactile spot from the palate of the alligator. There is no pigment, although the stratum corneum of the epidermis has blackened in the silver, except over the tactile spot. Beneath this rounded elevation there is a group of tactile cells with many delicate nerve fibers winding among them and ending on some of the cells. Between the tactile cells and the epidermis there is a broad band of colorless corium. Some of the nerve fibers cross this space to enter the epidermis. Below a large nerve trunk branches upward, sending three bundles to supply the tactile spot.



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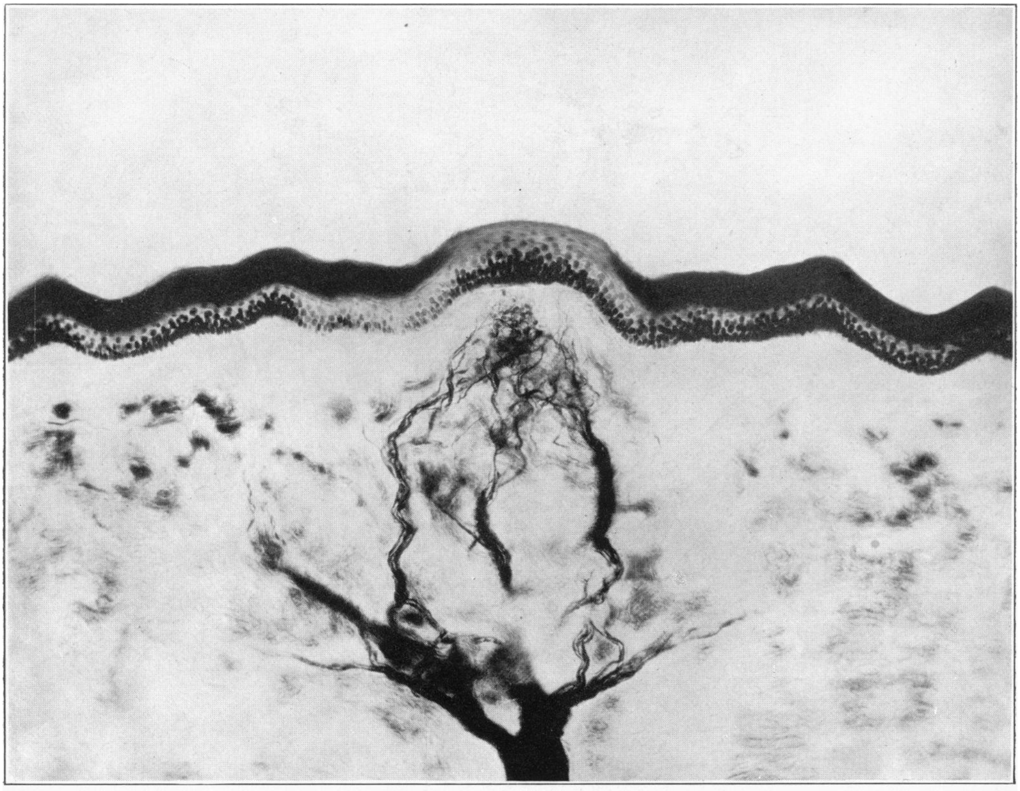

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