MELANIN IN THE INNER EAR *

DOROTHY WOLFF, M.A.
ST. LOUIS

REVIEW OF LITERATURE

The presence and distribution of melanin pigment in the labyrinth has long been recognized. In recent years, however, this fact has been overlooked by the authors of general textbooks of histology in their discussions of both pigment and the cytologic structures of the inner ear. English textbooks, in particular, have been remiss in this respect.

In 1851, Corti described pigment cells, resembling those of the choroid coat of the eye, in the "periosteum" (spiral ligament) of the cow and sheep. He observed pigment in amorphous grains and in enlarged epithelial cells of the stria in "very old" cats. It was also noted along the aqueduct of the cochlea and, in the cow and sheep, along the sheath of the auditory nerve.

As early as 1860, Voltolini of Breslau, in the first of a series of three reports on postmortem conditions of human ears, cited the presence of pigment in the cochlear spindle of a tuberculous patient aged 35. In the same article is the record of a tuberculous patient aged 37, in which it is definitely stated that no pigment was present. Pigment is not mentioned in the other three cases of the report. In his second article (1861), Voltolini reported four cases, in one of which a boy aged 16 showed a great amount of pigment in the three canals. In a man aged 65 with sarcoma in the internal auditory meatus, pigment was not mentioned. In 1863, Voltolini's third article appeared. In this he gave a description of fourteen cases, three of which showed pigment. In one of these patients, a man aged 81, pigment was found on the secondary tympanic membrane and most heavily on the spindle. A man aged 86 (whose death was due to heart failure and Pleuraerguss [pleural effusion]) showed pigment in the canals. Pigment was found in the saccule of a third patient whose age was not given and whose death was due to typhus.

In 1864, Lucae presented seven cases in a report similar to that of Voltolini, four of which showed pigment in the labyrinth. In a man aged 42, who died of tuberculosis, he observed much pigment where the nerve fibers spread out to the saccule and the ampullae, also along the cochlear spindle and Corti's membrane. He stated that the

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* From the Departments of Pathology and Otolaryngology of Washington University.

processes of these cells anastomosed with each other. In a man aged 47 with Bright's disease he observed round clumps of pigment in the spaces between Corti's fibers, and star-shaped branching cells on the wall of the saccule. Pigment was also observed in a man aged 70, who died of an infection in the knee joint, and in a man 50 years of age with tabes dorsalis. Lucae stated that the pigment might not be very important, as he had observed it in the rabbit. He did not think that it had a pathologic significance.

Von Rüdinger, in 1871, gave many illustrations of pigment cells in the vestibule and canals of amphibia. In discussing the human labyrinth, he said that Henle considered that the periosteum corresponded to the subarachnoid, and that perhaps that is why pigment cells are so scarce.

Waldeyer (1871) saw a strong connection between Corti's organ and the retina. He found the connective tissue walls or the ductus cochlearis and the choroid coat comparable, and he called attention to the similarity of the pigment cells in the ear and the eye.

In his detailed monograph, Retzius (1884) illustrated pigment cells and stated that he observed them in the human being on the vestibular membrane (Reissner's membrane). Reviewing Hasse's work on birds, he stated that pigment cells are lacking.

In 1901, Alexander made a detailed comparative study of the presence of pigment in many mammals. He found it present in most mammals in varying amounts. In one cat it was not found. (Unfortunately, the author does not state the color of the animals observed. One wonders whether the cat was the white cat that he has described elsewhere.) Pigment is found in the axial connective tissues of the cochlea in the human being, and in the endosteum of the scalae in the new-born infant and frequently in the adult. He found it also in the stria vascularis and in the connective tissue of the spiral ligament in the secondary tympanic membrane, in the vestibular floor, at the bases of the cristae maculae utriculi and sacculi and in the membrana vestibularis. He considered the pigment cells morphologically like those of the choroid coat. He presented excellent illustrations in color, showing pigment in various characteristic places in the labyrinths of various animals.

Siebenmann, in describing Reissner's membrane, stated that spindle-shaped cells with or without pigment had been observed. In describing the spiral sulcus, he observed that the epithelium is frequently pigmented. In the cochlea, suspended along the modiolus connective tissue, he noted cells of embryonic type resembling the arachnoid and bearing pigment.

Ranvier (1889) described pigment cells in the stria vascularis of the guinea-pig. He considered that they represent in the cochlear canal the homologue of the epithelial pigment of the retina; he presented a diagram to illustrate his point. He did not mention their presence in the vestibule.

Dawson (1925), in a comprehensive study of pigment in melanomas, failed to mention the presence of pigment in the labyrinth when discussing the general distribution of pigment in the body.

Few of the recent general textbooks on histology or pathology mention the inner ear in the list of pigment-containing organs of the body, such as the eye, the skin, the arachnoid of the brain and spinal cord, etc. Shambaugh (1927) made no mention of the presence of pigment in the labyrinth. Most of his illustrations seemed to be from other than human material. If a white animal was used it is probable that no pigment was present.

Jordan (1924) failed to mention the presence of pigment in the labyrinth. Lewis and Stöhr (1927) did not refer to it, nor did Bohm, Davidhoff and Huber (1920).

The most complete and accurate statements were made by W. Kolmer (1927). He stated that the amount of pigmentation in the region of the labyrinth depends on the general pigmentation of the animal. It is lacking in albino animals. In 1923, Eisinger found pigment in the sensory epithelium of the crista of the elephant. In the human being it is found especially in the modiolus, and increases with age. The cell bodies range in size from ⅓ to 3 microns. According to Alexander, pigmentation may be found in the bony vestibular canals, membrana tympani secundaria, epithelial wall of the sacculus, endosteal vessels and Reissner's membrane.

Maximow (1930) stated that branched melanophores are often encountered in the tissue of the utricle and saccule. The connective tissue of the spiral ligament also contains stellate connective tissue cells filled with pigment and other inclusions. The vestibular membrane sometimes contains pigment cells.

Even less informing are the textbooks devoted solely to the anatomy and diseases of the ear. Kerrison (1930) did not mention the existence of pigment in the labyrinth. Politzer (1926) briefly mentioned it and referred to Alexander's work. Henke and Lubarsch (1926) did not index the subject of pigment, but in the chapter by A. Eckert-Möbius the presence of pigment is discussed and the contributions of Rüdinger, Retzius and Alexander are mentioned. A. A. Gray (1907) observed that pigment is absent in human labyrinths, in many examples at any rate, and that it would be interesting to know whether pigment is found more abundantly in the labyrinth of the Negro than in that of white races; he said that probably no such investigation had ever been carried out.

OBSERVATIONS FROM THE OTOLOGY LABORATORY OF WASHINGTON UNIVERSITY

The observations thus far accumulated in the otology laboratory of Washington University are presented in order to call attention to this neglected subject. The summation of data from various investigators may lead to significant conclusions in the future.

The membranous labyrinths of twenty-eight human beings were examined microscopically, from sections cut 20 microns thick (with the exception of five embryos sectioned at 10 microns). Observations were also made on the monkey, rat, cat and rabbit. The race of the five embryos and one infant in the collection is unknown. The human specimens examined were from three 2 month embryos; three fetuses from 3 to 6 months old, two premature infants (6 months and 7 months, respectively), two stillborn infants and seventeen other persons ranging from 19 days to 59 years in age. The first table shows the findings in the embryos and fetuses. Table 2 shows the findings in the older specimens.

Table 1.—*Findings in Embryos and Fetuses*

Autopsy No.	Crown-Rump Length	Approximate Age	Pigment in Eye	Pigment in Ear	Pigment in Skin
XVI	7.2 cm.	4 months	+	—	—
XVII	15.15 cm.	6 months	?	—	—
36	15 mm.	2 months	+	A few red-staining inclusions, shaped somewhat like pigment cells	—
37	21 mm.	3 months	+	—	—
49	20 mm.	2+ months	+	—	—
124	17 mm.	2 months	+	—	—

The observations in table 1 would indicate that pigment in the eye appears earlier than at 4 months, as stated by Spencer. Observations were made on the skin in these cases in view of the statement of Dawson that in the fair races all basal cells are pigmented at birth and that in the fetus all the basal cells are pigmented for a long time; later a depigmentation occurs. In the present specimens it will be noted that no pigment was found in the skin, even in a 6 months premature Negro infant that lived one day.

Of the thirteen specimens showing pigment, five were from Negroes and eight from white persons. It is interesting to note that all the Negroes examined showed a heavy deposit of pigment, with the exception of one 6 months premature infant which gave negative results. Pigment had probably not yet formed.

Those showing pigment ranged from two stillborn infants to persons 59 years of age. Of the white persons not showing pigment none was older than 10 years. It is conceivable that if it could be applied, the "dopa" reaction might exhibit pigment in these apparently negative specimens.

The relation of the deposit to sex is as follows: In males, eight of eleven showed pigment; in females, five of ten. Of those who did not show pigment two were males and five females.

In all cases in which both ears were examined, the condition—either positive or negative—was found to be bilateral.

TABLE 2.—*Findings in Older Specimens*

Autopsy No.	Pigment	Fixative*	Race	Sex	Age	Diagnosis
I	—	Form.	?	?	?	Congenital syphilis
XVI	—	Z–F	W	F	7 months (premature)	
3849	—	Form.	W	M	19 days	Congenital atresia of the esophagus
3865	+	Form.	W	M	4 months	Congenital syphilis; otitis media; thrush; spleen the size of an adult's (10.5 by 0.5 by 1 cm.); weight, 60 Gm.; pulp soft
3869	—	Form.	W	F	11 weeks	Spina bifida; operation for meningocele
3873	+	Form.	W	F	3½ months	Purulent bronchitis; splenomegaly; bronchopneumonia; congenital syphilis
3878	—	Form.	W	F	15 months	Peritonitis; bronchopneumonia; edema of the brain
3884	+	Z–F	W	M	36 years	Multiple areas of cerebral softening; several arachnoid cysts found at operation
3887	—	Zenk.	N	M	1 day (6 months premature)	Prematurity; atelectasis; hemorrhage beneath skin; congenital malformation of the brain
3894	+	Z–F	W	M	51 years	Spongioblastoma multiforme
3903	+	Form.	W	M	8 years	Fracture of skull
3920	+	Z–F	W	F	5½ months	Hydrocephalus (acquired)
3923	+	Form.	N	M	10½ months	Sympatheticoblastoma of suprarenal; metastases to skull, ribs and mediastinal lymph nodes
3924	+	Form.	N	M	Stillborn	
3937	+	Zenk.	W	F	Stillborn	Icterus; massive hemorrhage in gastro-intestinal tract
3947	+	Zenk.	N	F	7 months	Influenzal meningitis
3948	+	Form.	N	M	13 years	Ewing's sarcoma of the right fibula; metastasis to the skull, vertebrae and ribs
3951	—	Zenk.	W	F	5 years	Streptococcus meningitis
3953	+	Zenk.	W	M	59 years	Carcinoma of larynx
3956	—	Zenk.	W	F	10 years	Lateral sinus thrombosis from mastoiditis
3967	—	Form.	W	M	2 months	Congenital hydrocephalus
4106	+	Form.	N	F	1 year	Tuberculous meningitis

* Form., formaldehyde; Zenk., Zenker's solution; Z–F, both solutions.

In the belief that some correlation might exist between the presence of pigment in the labyrinth and its occurrence elsewhere in the body, an examination was made of sections taken from other regions. Sections of the brain, skin, suprarenal gland and spleen were sought in particular. The results do not merit report, as the tissues were not taken uniformly, no such problem being in mind at the time of autopsy. It may be said, however, that pigment was found in the arachnoid over the brain stem when no pigment had been reported in the cochlea, and vice versa.

The animals studied included five monkeys, two albino rats, one rabbit and three cats. The monkeys were all of the species *Macacus rhesus* and were sectioned at 20 microns. In all of these, pigment was observed. No pigment was found in the albino rats, as was to be expected. Of the cats, two were late fetuses and showed no pigment. The third was an adult cat, almost entirely black. One ear was examined by the dissection method which proved rather unsatisfactory for the exact location of the pigment found. The other ear will be prepared for serial sections. Material for observations is being collected from blue-eyed white rabbits and guinea-pigs.

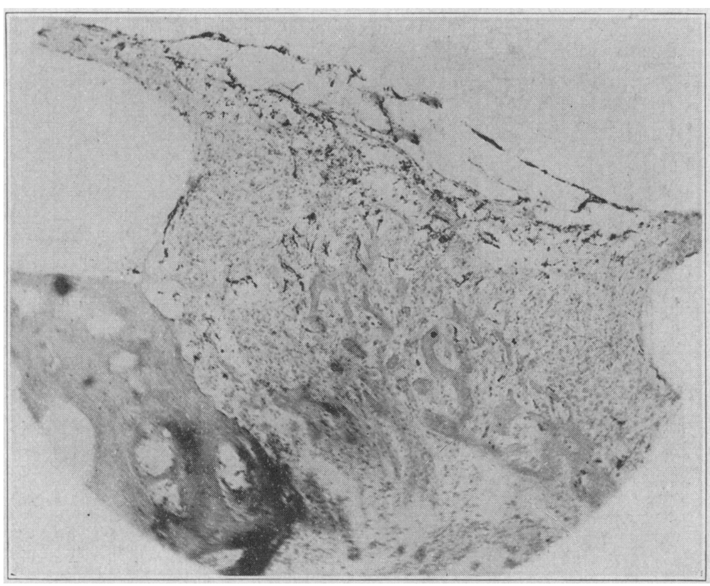

Fig. 1 (autopsy 3894).—Distribution of pigment on the modiolus; × 50.

DISTRIBUTION OF PIGMENT IN THE INNER EAR

In the human material under consideration, the modiolus is found to show more abundant pigment than any other region. If pigment occurs at all, it is always present on the modiolus. Here it lies in the delicate connective tissue cells in the interstices of the cribriform area and along the connective tissue forming the proximal wall of the scalae. The amount is generally greater along the modiolar wall of the scala vestibuli than along the modiolar wall of the scala tympani. If the amount present is slight, it will be found along the scala vestibuli and not along the scala tympani. If the amount of pigmentation is very small, the chromatophores may be seen only along the bony wall instead of in the membranous meshwork, and appear to accompanv the modiolar artery. When less dense, the pigment appears as fine granules within the primitive branched connective tissue cells.

In cases of heavy pigmentation the melanin may be seen along the lamina spiralis ossea, almost to the labium spiralis. On these delicate bony trabeculae, it appears to cling to the periosteum. It never occurs among the spiral ganglion cells and rarely close to the nerve fibers. In the specimens examined, it was not found (as reported by earlier observers) in typical bone marrow spaces, but only in the interstices in the bone through which nerve fibers pass, or in those filled with delicate areolar tissue, such as is commonly seen in sections of the temporal bone. In only one specimen, in one place, did the pigment appear on

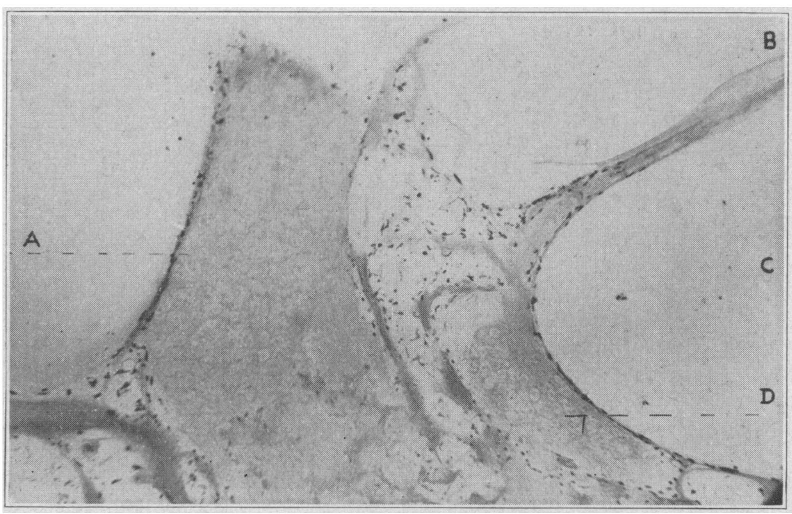

Fig. 2 (autopsy no. 3923).—Photomicrograph showing how the deposition of pigment avoids the region of the ganglion cells. *A* indicates ganglion; *B*, scala vestibuli; *C*, scala tympani, and *D*, ganglion; × 50.

the bone. This was probably a surface cut of an interface of the bone, over which a branch of a melanophore happened to pass.

Besides being found in the cochlea, pigment was also observed in the interstices of bone through which the branches of the vestibular nerve pass to their terminations. It frequently occurs at the base of the maculae utriculi and sacculi and at the bases of the cristae in the characteristic manner so well illustrated by Alexander. In two persons, one Negro and one white, it was observed in the round window membrane.

Sometimes pigment was observed at the bases of the ampullae of the superior and horizontal canals and not at that of the posterior canal. Sometimes the pigmentation of the horizontal canal appeared heavier than that of the superior canal. Perhaps these differences may be related to the route of the blood supply.

Pigment also occurred along the wall of the cisterna perilymphatica, and in one case it was observed along the wall of the endolymphatic duct. In only one case was it seen on Reissner's membrane. This is significant, as its occurrence here and in the stria would seem to be rather common, according to some authors. Perhaps the fact that the delicate Reissner's membrane was cut in cross-section in the present

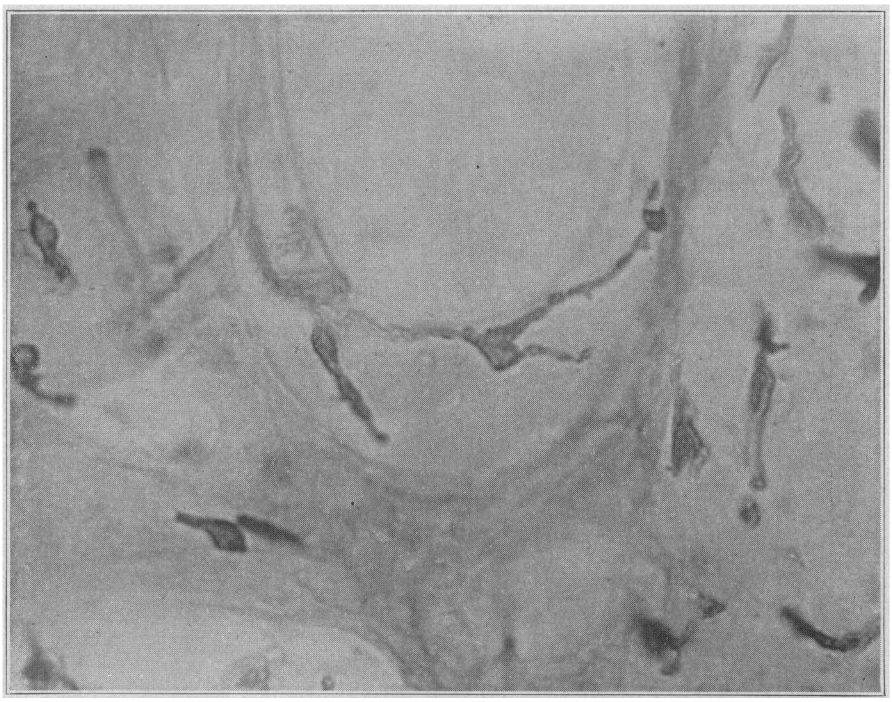

Fig. 3.—Individual pigment cells as seen under high power.

specimens and never seen in surface view makes these chromatophores less readily observed. Actual large branching chromatophores were not found in the spiral ligament, though granular pigment was observed, especially along the stria vascularis.

Pigment was not found along the facial nerve or along the eighth nerve in the internal auditory meatus.

The distribution of pigment in animals seems to differ in certain respects from that in man. In none of the lower mammals examined was it ever observed in the delicate connective tissue within the interstices of the cribriform modiolus. (A marked anatomic difference between the monkey and man was noted in this region. The nerve fibers in the monkey completely fill the canals in which they travel, leaving no space for loose areolar tissue to surround them. The interstices through which the cochlear blood vessels pass, however, are well surrounded by the perivascular connective tissue, but even in this region no pigment was observed.) Pigment was not found in the lower mammals along the medial wall of either the scala tympani or the scala vestibuli. In all animals in which it was found, it occurred along the stria vascularis. In the monkey it could be observed only under high power

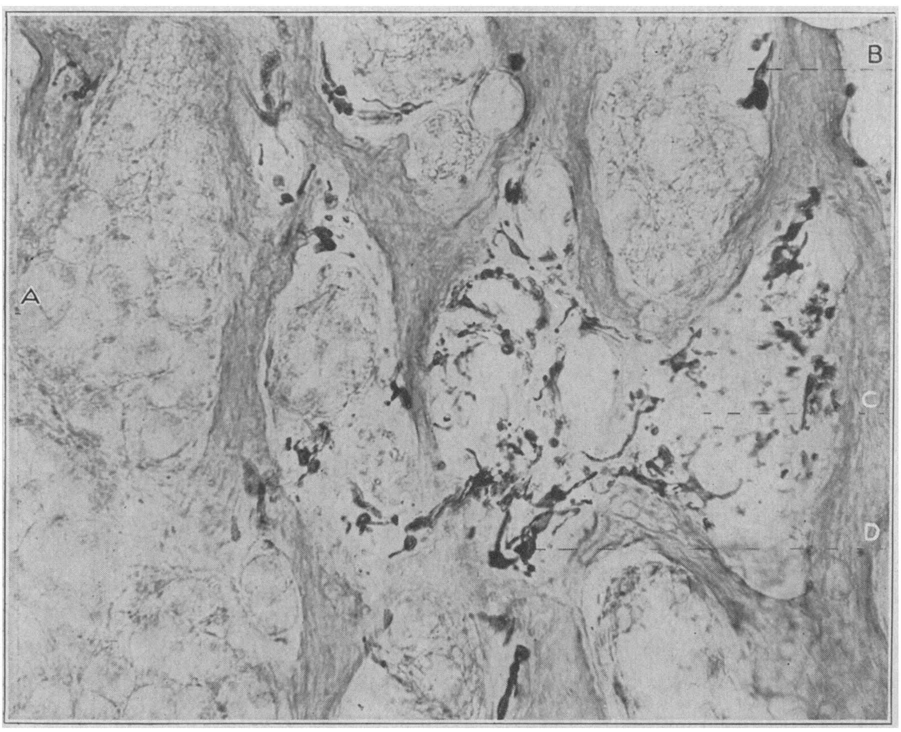

Fig. 4 (autopsy 3948).—Distribution of pigment in perivascular and perineural spaces of the modiolus. *A* indicates cochlear neurons; *B*, perineural space; *C*, perivascular space, and *D*, pigment.

magnification. In one monkey it was found dispersed in fine granules along Reissner's membrane. (It was not observed in Reissner's membrane even in the heavily pigmented specimens from human beings.) It was observed in the perilymphatic tissue below the level of the cristae of the horizontal and superior ampullae.

The pigment observed in the rabbit was relatively heavier than that observed in the monkey, although the animal was a mixed white and New Zealand red.

THE CHARACTER OF PIGMENT CELLS

Human specimens showing an abundance of pigment exhibit large, irregularly branched chromatophores the "antler-like" processes (Loeb) of which seem to anastomose with each other. They are easily discernible under low power magnification. It is readily conceivable that they may even form a continuous network similar to that which is thought to exist in the subcutaneous pigment of amphibia. The thick celloidin sections (20 microns) make the study of these chromatophores

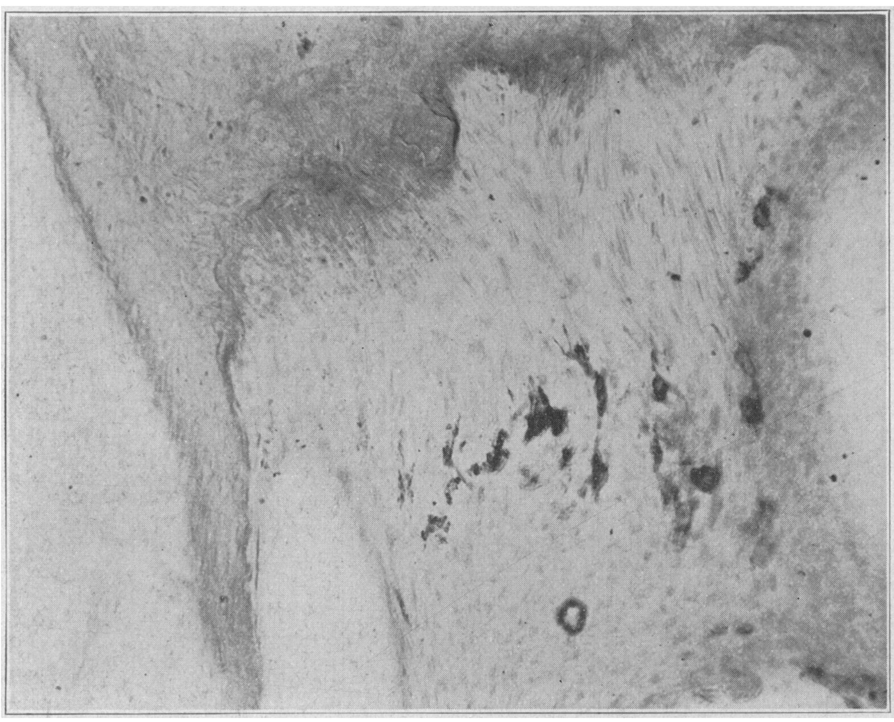

Fig. 5.—Pigment at the point of attachment of the round window membrane.

much more informing than thinner sections. By focusing, it is possible to trace the ramifications of the processes. These twist in more or less regular spirals, as one may see by following the parallel rows of granules. The branching in the arachnoid of the brain is not nearly so evident in the specimens examined, even though some sections were also cut at 20 microns.

In places the chromatophores may appear as pale yellow branched cells, slightly granular. They frequently appear to have grown like an amorphous crystal. Perhaps they can better be likened to the budded branches seen on a copper sulphate crystal when it is immersed in a solution of potassium ferrocyanide. It is difficult to say whether they grow these branches by the absorption of water—as chromatophores—or whether the processes are those of the connective tissue cells merely made visible by the presence of melanin. The cell bodies averaged 2 microns in length, and with their processes, they averaged 73 microns.

Sometimes granules of pigment may be seen peripherally located in the large round wandering cells. The pigment was found to be slightly soluble in hydrogen peroxide. Sections left in this solution for twenty-four hours showed fewer chromatophores, and those still present were light yellow instead of the dark brown characteristic of heavily pigmented

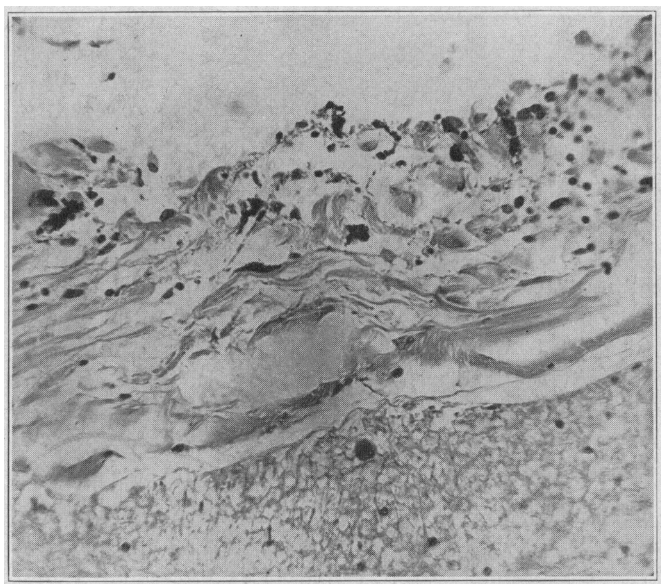

Fig. 6.—Pigment in the arachnoid of the cord.

specimens. After forty-eight hours most of the pigment cells had become completely invisible, and the ones that remained were pale yellow.

Pigment cells in the lower mammals differ from those in man in that the cells have more rounded bodies and fewer anastamosing branches. In many instances the pigment was dispersed in diffuse granules, no single cell type appearing as its bearer. In the monkey large ameboid-looking pigment cells were sometimes observed in the stria. These measured 5.8 microns. The granules were much coarser than those of the human being, but like the latter tended to aline themselves in parallel rows. Pigment cells found in the epidermis of the external auditory meatus in the monkey appeared to be shaped much more like those in the human cochlea.

In the rabbit huge globular cells, 10 microns in diameter, were present along the stria as bearers of pigment. Diffuse granules were also present. Branched pigment cells occurred at the bases of the maculae.

THE SIGNIFICANCE OF PIGMENT IN THE INNER EAR

The significance of melanophores in the labyrinth is not known. They may merely represent an embryonic remnant of a primitive pigmented vascular sheet (Acton) or revert to a time when the central

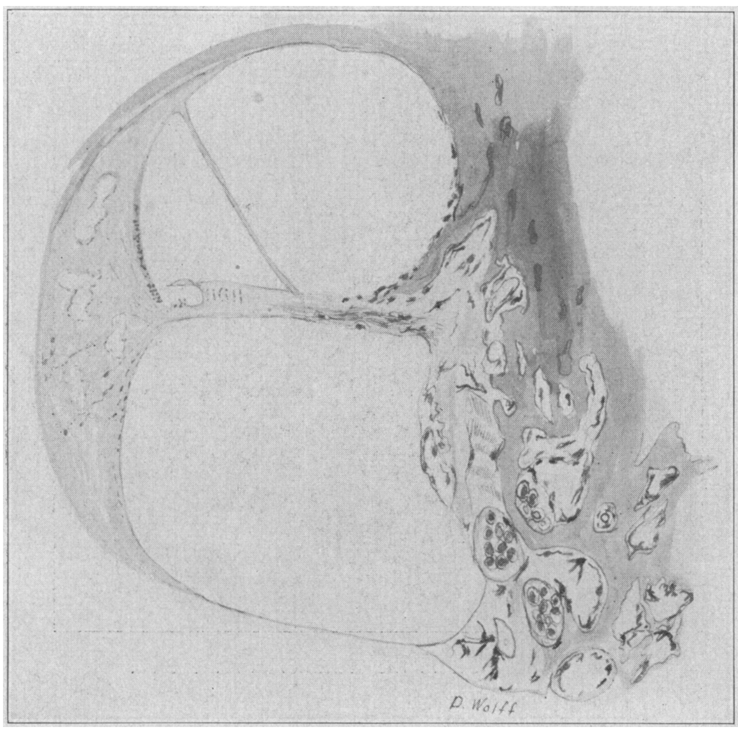

Fig. 7.—Distribution of pigment in one turn of the cochlea. (Water color.)

nervous system as a whole was encased in a pigmented sheath. Such a theory alone would correlate the occurrence in the brain, eye, ear, suprarenal gland and skin. No one can have been a student at Woods Hole without having observed and been fascinated by the varied chromatophores of the marine forms: the red pigment granules of the chorion of the sand dollar; the varicolored (red, yellow, blue, etc.) chromatophores of the developing squid, appearing and disappearing, and the melanophores of the fundulus, controlled, as Wyman described, by the nervous system. Do those of the squid represent some constantly reversible chemical action? They act like the play of an electric current.

VIEWS ON THE NATURE OF MELANIN

Arey, in speaking of the melanophores of the eye, said: "It is puzzling to determine whether the pigment processes are protruded and withdrawn like pseudopodia, or whether pigment granules flow into the processes."

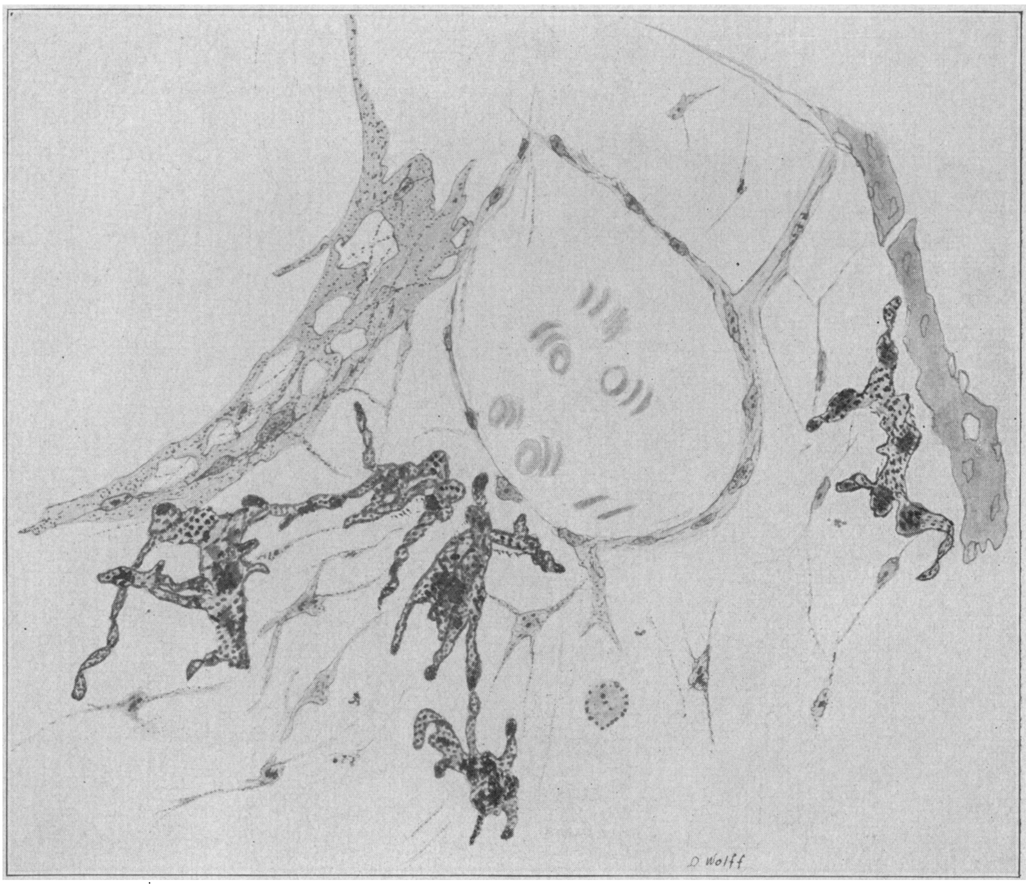

Fig. 8.—Pigment cells as seen in perivascular tissue of the modiolus. Oil immersion. (Water color.)

Bruno Bloch, professor of dermatology at Zurich, has extracted a substance—dioxyphenolalanin (dopa)—from the embryo of the broad bean. Frozen sections of fresh tissue treated with a 1:1,000 solution of dopa will exhibit melanin where melanogen, its forerunner, is present. This reaction, according to Spencer, does not occur in melanophores but only in melanoblasts, melanophores being the connective tissue bearers of pigment while melanoblasts are the manufacturers of melanin.

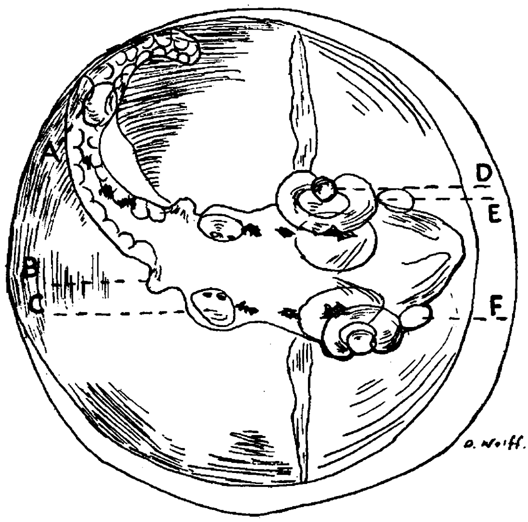

Fig. 9.—Fundulus heteroglitus (5 day fetus), showing yolk almost consumed; also alinement of pigment granules. *A* indicates Kupffer's vesicle; *B*, gill slit bud; *C*, otic capsule; *D*, lens; *E*, eye, and *F*, nasal capsule.

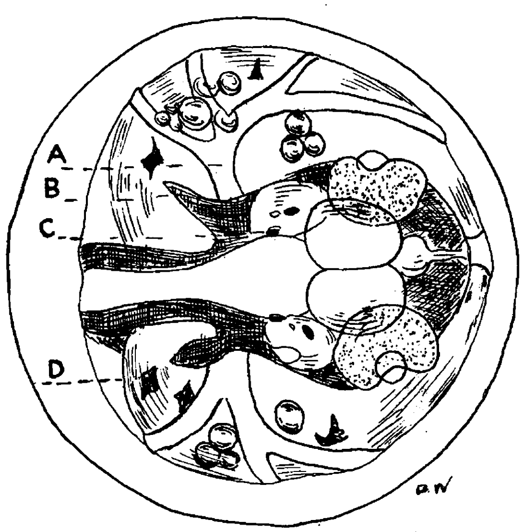

Fig. 10.—Fundulus majalis (7 day fetus), showing a decrease in the size of the yolk. *A* indicates the vitelline arteries; *B*, gill fringe; *C*, otolith, and *D*, pigment cell.

Melanin is believed by Bloch to be a protein-derived substance which is transformed by an enzyme oxydase into melanin. Gortner (1911) expressed the belief that there are two kinds of melanin. The melanoproteins are those soluble in weak acids and are not commonly found in pigment granules, though Gortner found them in auburn hair. The pigment granules that are not soluble in weak acids are oxidized from a different chromogen than melanoproteins.

The following paragraph is an abstract presenting the views of Pryde (1928) in regard to the chemical nature of melanin: The constitution of melanin remains undetermined. According to the Dumas

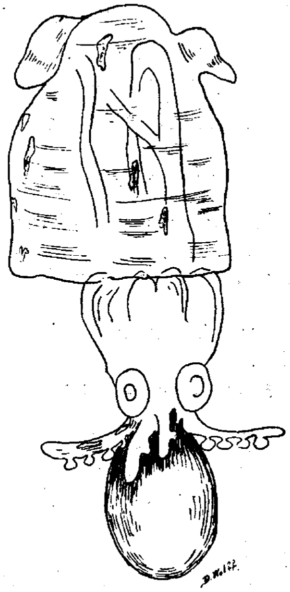

Fig. 11.—Developing squid with red and blue chromatophores.

methods it contains 8.65 per cent nitrogen. Tyrosinase is an oxidizing enzyme widely distributed in vegetable tissues. Its specific substrate is the amino-acid tyrosine which, in contact with the enzyme and in the presence of atmospheric oxygen, is oxidized ultimately to a black pigment melanin. When tyrosine acts on tyrosinase, a series of color changes occurs before the black insoluble melanin separates from the solution. First, at a p_H of from 6 to 8 a red pigment is formed, probably quinone. This is in turn decolorized and then oxidized to form melanin.

CONCLUSIONS

1. The membranous labyrinth should be included in the list of depots for branched melanophores along with the retina and choroid coats of the eye, the arachnoid of the brain and cord, the epidermis, etc.

2. In human embryonic life, pigment does not appear in the ear as soon as it appears in the eye.

3. Melanin was not found in the human fetal skin up to 6 months—not even in the Negro.

4. All Negroes, including stillborn infants, show pigment in the labyrinth. The age when it first appears is not yet known.

5. Among white persons more males than females show pigment.

6. In human beings the heaviest pigmentation is along the medial wall of the scala vestibuli and in the interstices of the cribriform modiolus.

7. In human beings the pigment is contained in large branching, anastomosing, connecting tissue-like cells.

8. In the animals examined, pigment occurs in the stria vascularis, if at all, and never in the interstices of the modiolus.

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