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Anatomy and Embryology

The Timing and Sequence of Events in the Development of the Human Eye and Ear During the Embryonic Period Proper*

Ronan O'Rahilly
Carnegie Laboratories of Embryology, California Primate Research Center, and Departments of Human Anatomy and Neurology, University of California, Davis, California 95616, USA

Summary. A documented scheme of the early development of the human eye and ear is presented. It is based on (1) reports of workers who personally studied staged embryos, and (2) personal observations and confirmations. The necessity of using staged embryos in order to determine the precise sequence of developmental events is stressed.

Key words: Human embryo – Developmental stages – Eye – Ear – Otocyst

Introduction

Although interest in the development of the sense organs may be traced back to Aristotle's description of the eye of the chick embryo, understanding of the events involved began only during the 19th century. That the optic vesicle is derived from the forebrain was established in 1817 by Pander and was followed by a series of equally important discoveries (Adelmann 1966): the lens arises from the surface ectoderm (Huschke in 1830); the optic cup is formed from the optic vesicle (Huschke in 1835); the lens epithelium and fibres develop from the lens vesicle (Remak in 1850–1855); the retina is formed from the two layers of the optic cup (von Kölliker in 1861); the optic nerve fibres arise in the retina and grow into the brain (Müller in 1875). The experimental basis of lens induction (reviewed by McAvoy 1980) had to await the work of Spemann, chiefly between 1904 and 1912.

In this century, detailed accounts of the development of the human eye have been provided by Keibel (1912), Bach and Seefelder (1914), Dejean et al. (1958), Duke-Elder and Cook (1963), and Mann (1964). The only work based on stage material, however, is that of O'Rahilly (1966, 1975).

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In 1831, Huschke discovered that the membranous labyrinth developed from a pit in the surface ectoderm (Streeter 1918). Accounts of the development of the human ear, however, have been neither as numerous nor as thorough as those of the eye. Much valuable information on unstaged material can be found dispersed throughout the monograph by Bast and Anson (1949). Since the publication of that work, Anson and his collegues have published a large number of articles on the (chiefly fetal) development of the temporal bone, tympanic ring, and auditory ossicles (e.g., Hanson et al. 1962). Little is available on staged specimens, other than the limited account by O'Rahilly (1963).

Material and Methods

The scheme presented here is based on first-hand reports of workers who personally studied staged human embryos, supplemented by personal observations and confirmations of the present writer. Only staged embryos have been considered, that is, those specifically assigned to one of the recognized Carnegie stages (O'Rahilly 1979). Certain early embryos, the stages of which were not specified, have here been assigned to stages on the basis of their somitic count. Moreover, Carnegie embryos that were described prior to the establishment of the staging system have since been staged.

Results

Sequence of Events during Early Development of the Human Eye

Stage 10 (ca. 2–3.5 mm; 4–12 pairs of somites; ca. 22 days)

The optic primordium and the optic sulcus appear in the prosencephalic fold at 8 pairs of somites (Bartelmez 1922; Bartelmez and Blount 1954; Bartelmez and Dekahan 1962).

The optic primordia meet at the torus opticus, or chiasmatic ridge (Bartelmez and Blount 1954).

Stage 11 (ca. 2.5–4.5 mm; 13–20 pairs of somites; ca. 24 days)

The optic evagination is produced at the optic sulcus at about 14 pairs of somites, and the optic ventricle is continuous with that of the forebrain (Streeter 1942, Fig. 6; O'Rahilly 1966, Fig. 3).

The lateral wall of the evagination is at first in contact with the surface ectoderm (Bartelmez and Blount 1954).

The wall of the optic evagination contributes neural crest to its mesenchymal sheath from about 14–16 pairs of somites onwards (Bartelmez and Blount 1954, plate 5). The sheath then separates the evagination from the overlying ectoderm.

The optic evagination constitutes the optic vesicle at approximately 17–19 pairs of somites (O'Rahilly 1966, Fig. 3).

The caudal limiting sulcus develops between the optic evagination and the forebrain (O'Rahilly 1966, Fig. 3).

Stage 12 (ca. 3–5 mm; 21–29 somites; ca. 26 days)

The optic neural crest reaches its maximal extent and the optic vesicle becomes covered by a complete sheath, giving the appearance of a "frightened hedgehog" (Bartelmez and Blount 1954).

Stage 13 (ca. 4–6 mm; 30 or more pairs of somites; ca. 28 days)

The optic vesicle is covered by a basement membrane, and the surface ectoderm is lined by a basement membrane (O'Rahilly 1966, Fig. 10).

The retinal disc (future inverted layer of optic cup) and lens disc appear and are in contact (O'Rahilly 1966, Figs. 20 and 21).

A marginal zone becomes detectable in the retinal disc (O'Rahilly 1966, Fig. 22).

The primordia of the lateral and superior recti appear (Gilbert 1957).

Stage 14 (ca. 5–7 mm; ca. 32 days)

A uveocapillary lamina (O'Rahilly 1966) becomes defined.

The retinal disc is invaginated and so the optic cup is formed (Streeter 1945, Fig. 5; O'Rahilly 1966, Fig. 23).

The retinal ("choroid") fissure is delineated (Streeter 1951, Fig. 2).

The inverted layer of the optic cup comprises a terminal bar net (future external limiting membrane), proliferative zone (mitotic phase), primitive zone (intermitotic phase), marginal zone, and an internal limiting membrane (O'Rahilly 1966, Fig. 26). The developing cerebral stratum of the retina is closely comparable to the developing cerebral wall (O'Rahilly 1975, Fig. 9).

The lens disc becomes indented and so the lens pit is formed. Cell remnants are extruded into the lens pit (O'Rahilly 1966, Figs. 24 and 25).

The oculomotor nerve appears (F. Müller, personal communication).

The primordia of the superior rectus and superior oblique appear (Gilbert 1957).

Condensations for the insertions of the recti appear peripherally and probably contribute to the sclera later (ibid.).

Stage 15 (ca. 7–9 mm; ca. 33 days)

The optic cup at stages 14–16 measures approximately 0.2–0.35 mm in diameter (O'Rahilly and Bossy 1972).

Retinal pigment appears in the external layer of the optic cup (O'Rahilly 1966, Fig. 29).

The primary vitreous body begins to form in the lentiretinal space (O'Rahilly 1966).

The hyaloid artery enters the lentiretinal space through the retinal fissure (ibid.).

The lens is surrounded by the lens capsule (O'Rahilly 1966, Fig. 10).

The lens pit has closed and so the lens vesicle is formed (Streeter 1945).

The lens body appears and consists of early lens fibres (O'Rahilly 1966, Fig. 28).

The restored surface ectoderm constitutes the anterior epithelium of the future cornea (O'Rahilly 1966, Fig. 27), which has its own basement membrane.

The trochlear and abducent nerves appear (F. Müller, personal communication).

The oculomotor and abducent nerves grow to the respective condensations for their muscles (Gilbert 1957).

Stage 16 (ca. 8–11 mm; ca. 37 days)

Eyelid grooves appear (Pearson 1980).

The rim of the optic cup is pentagonal (Streeter 1951; Fig. 2; O'Rahilly 1966) and five notches (S, a, b, c, d) are present.

The lips of the retinal fissure may be in contact or may even be fused (Streeter 1951, Fig. 2).

The optic stalk is definite (O'Rahilly 1966).

Perilental blood vessels (tunica vasculosa lentis) are visible (ibid.).

The lens cavity is D-shaped in section (O'Rahilly 1966, Fig. 30).

The ciliary ganglion is present (Woźniak and O'Rahilly 1980).

The trochlear nerve grows to the condensation for the superior oblique (Gilbert 1957).

The primordium of the medial rectus and the common primordium of the inferior rectus and inferior oblique appear (Gilbert 1957).

Stage 17 (ca. 11–14 mm; ca. 41 days)

Eyelid folds develop at stages 17–19 (Pearson 1980).

The optic cup measures approximately 0.5 mm in diameter (O'Rahilly and Bossy 1972).

A notch for the retinal fissure may persist anteriorly (Streeter 1951, Fig. 2).

An internal neuroblastic layer is formed by internal migration into the marginal zone of the retina (O'Rahilly 1966, Fig. 38). The marginal zone then constitutes the transient fibre layer (of Chievitz) (ibid.).

The retina comprises the proliferative zone, external neuroblastic layer, transient fibre layer, and internal neuroblastic layer (ibid.).

Radial fibres (of Müller) appear probably between stages 14 and 17 (ibid.).

The cavity of the lens vesicle gradually changes on section from D-shaped to crescentic (O'Rahilly 1966, Figs. 31 and 32).

The row of lens nuclei is changing on section from a circle to a D to a nuclear bow (Streeter 1948, Figs. 29, 30, and 32).

An instance of cyclopia at stage 16 or 17 has been reported (Mall 1917).

Stage 18 (ca. 13–17 mm; ca. 44 days)

The eyelids may begin to be visible, and also the grooves initiating the conjunctival sacs (Streeter 1948).

The internal neuroblastic layer of the retina is U-shaped (O'Rahilly 1966).

The hyaloid system is well developed (Streeter 1951, Fig. 3).

The cavity of the lens vesicle is becoming obliterated by primary lens fibres (Streeter 1948, Fig. 31).

Mesenchyme invades the interval between the lens epithelium and the surface ectoderm, and possibly the posterior epithelium of the cornea (the mesothelium of the anterior chamber) is forming (Streeter 1948, Fig. 31).

An instance of cyclopia has been described (Orts Llorca 1955).

Stage 19 (ca. 16–18 mm; ca. 48 days)

The eyelid folds develop into eyelids and the upper and lower eyelids meet at the lateral canthus (Pearson 1980).

The lips of the retinal fissue are temporarily everted near the optic stalk (O'Rahilly 1966, Fig. 45).

The internal neuroblastic layer of the retina encircles the entrance of the hyaloid artery to the globe (O'Rahilly 1966, Fig. 12).

Ganglion cells give rise to optic nerve fibres (O'Rahilly 1966, Fig. 46).

The posterior epithelium of the cornea is distinguishable (O'Rahilly 1966, Fig. 44).

Stage 20 (ca. 18–22 mm; ca. 51 days)

The medial canthus is established (Pearson 1980).

The optic cup measures approximately 1 mm in diameter (O'Rahilly and Bossy 1972).

Nerve fibres are clearly visible in the retina and they reach the brain (O'Rahilly 1966).

The cavity of the optic stalk is obliterated (O'Rahilly 1966, Fig. 49).

The lens cavity is obliterated and a lens suture begins to form (O'Rahilly 1966).

The developing cornea comprises the anterior epithelium, an acellular postepithelial layer (future substantia propria), and the posterior epithelium (ibid.).

The trochlea for the superior oblique begins to form at stages 20 to 23 (Gilbert 1957).

Stage 21 (ca. 22–24 mm; ca. 52 days)

Cells begin to invade the postepithelial layer of the cornea, converting it into the substantia propria (O'Rahilly 1966).

The levator palpebrae superioris arises by delamination from the superior rectus at stages 21 to 23 (Gilbert 1957).

Stage 22 (ca. 23–28 mm; ca. 54 days)

The eyelids are rapidly encroaching on the globe (Streeter 1951).

A scleral condensation is now definite (Gilbert 1957).

Bergemeister's papilla (a clump of cells surrounding the exit of the hyaloid artery from the optic nerve) is present in some eyes (O'Rahilly 1966).

The "amas stratifié" (the peripheral condensation of the posterior epithelium), pupillary membrane, and anterior chamber develop (ibid.).

The cellular invasion of the postepithelial layer of the cornea is complete centrally in some eyes (ibid.).

Stage 23 (ca. 27–31 mm; ca. 57 days)

The eyelids are still open (Streeter 1951, Fig. 76), contrary to the statement of Pearson (1980).

The optic cup measures approximately 1.5–2 mm in diameter (O'Rahilly and Bossy 1972) and the lens approximately 0.5–1 mm.

The retina comprises the pigmented layer, external limiting membrane, proliferative zone, external neuroblastic layer, transient fibre layer, internal neuroblastic layer, nerve fibre layer, and internal limiting membrane (O'Rahilly 1966, Fig. 53).

The secondary vitreous body is forming (O'Rahilly 1966, Fig. 56).

Secondary lens fibres are forming (O'Rahilly 1966).

The cornea comprises the anterior epithelium and its basement membrane, the substantia propria, and the posterior epithelium (Streeter 1951, Fig. 6; O'Rahilly 1966, Fig. 59).

An instance of synophthalmia has been described (Orts Llorca 1955).

Sequence of Events during Early Development of the Human Ear

Stage 9 (ca. 1.5–2.5 mm; 1–3 pairs of somites; ca. 20 days)

The otic disc (or, at least, the otic zone) first appears opposite the rhombencephalic fold (Bartelmez 1922; Ingalls 1920; Ludwig 1928; O'Rahilly 1963, plate 1, Fig. A).

Stage 10 (ca. 2–3.5 mm; 4–12 pairs of somites; ca. 24 days)

A marginal velum covered by a terminal bar net appears superficially in the otic disc (O'Rahilly 1963, plate 1, Fig. B) and the first indication of invagination is observed at 10 pairs of somites (Corner 1929).

Possibly some cells are migrating from the otic disc at 12 pairs of somites (Bartelmez and Evans 1926).

Facial (so called acousticofacial) crest is forming in the rhombencephalic fold (Bartelmez 1922; Bartelmez and Evans 1926).

Stage 11 (ca. 2.5–4.5 mm; 13–20 pairs of somites; ca. 24 days)

The otic disc becomes invaginated progressively (Streeter 1942, Fig. 8) so that the otic pit is formed (O'Rahilly 1963, plate 1, Fig. C).

The otic disc attains its position dorsal to the second pharyngeal cleft at 16 pairs of somites (Bartelmez and Evans 1926).

Stage 12 (ca. 3–5 mm; 21–29 somites; ca. 26 days)

The otic vesicle is forming and its cavity communicates with the surface by a narrow pore (Streeter 1942, Fig. 8; O'Rahilly 1963, plate 1, Fig. 1). The vesicle is visible in the intact embryo (Streeter 1942, plate 1).

The ventral wall of the otic vesicle contributes to the vestibulocochlear crest (Politzer 1956; O'Rahilly 1963, plate 1, Fig. D; see also Theiler 1949).

Stage 13 (ca. 4–6 mm; 30 or more pairs of somites; ca. 28 days)

The otic vesicle is surrounded by the basement membrane of the otic disc (O'Rahilly 1963).

A capillary network is being laid down around the otic vesicle and, in the more advanced embryos, the mesoderm is beginning to become condensed as the otic capsule (Streeter 1945).

The otic vesicle, or otocyst, becomes closed from the surface (Anson and Black 1934; Streeter 1945, Fig. 9).

The remains of the connecting stalk may in some cases be seen as a projection on the wall of the otic vesicle (O'Rahilly 1963, plate 1, Fig. F) and/or on the surface ectoderm (ibid., Fig. E).

The dorsomedial portion of the otic vesicle can be distinguished as the endolymphatic appendage (Streeter 1945).

The vestibular part of the vestibulocochlear ganglion and vestibular nerve fibres dan be distinguished (F. Müller, personal communication).

Stage 14 (ca. 5–7 mm; ca. 32 days)

The endolymphatic appendage is becoming tapered and the ventral portion of the otic vesicle is becoming elongated to form the cochlear duct (Streeter 1945).

Stage 15 (7–9 mm; ca. 33 days)

The otic capsule is represented by condensed mesenchyme (Streeter 1917, Fig. 2).

The utriculo-endolymphatic fold is pronounced (O'Rahilly 1963).

Vestibular nerve fibres extend from the ganglion to the epithelium of the otocyst (F. Müller, personal communication; Yokoh 1971).

The auricular hillocks are visible in the more advanced embryos (Streeter 1948).

The most ventral segment of the second pharyngeal arch (hyoid bar) is the primordium of the antitragus (Streeter 1948).

Stage 16 (ca. 8–11 mm; ca. 37 days)

Thickenings in the wall of the main, or vestibular, portion of the otic vesicle presage the appearance of the semicircular ducts (Streeter 1948; O'Rahilly 1963).

A utriculosaccular diverticulum is distinguishable (Streeter 1906, plate 1, Fig. f).

The spiral ganglion is visible (Streeter 1906, Fig. 5).

A reconstruction of the blastemal mass for the stapes has been published (Hanson et al. 1962, Fig. 1). It also shows the stapedial artery.

Auricular hillocks representing the tragus, crus helicis, helix, and antitragus are present (Streeter 1948).

Stage 17 (ca. 11–14 mm; ca. 41 days)

The otic capsule consists of dense mesenchyme, which is near chondrification (O'Rahilly and Müller 1983).

Portions of the wall of the vestibular part of the otic vesicle are becoming thinner prior to cellular disintegration, but no semicircular duct is yet present (Streeter 1948).

The geniculate ganglion is established (F. Müller, personal communication).

The tubotympanic recess and chorda tympani are visible in reconstructions (Blechschmidt 1963, plates 25 and 26).

Reconstructions of the auditory ossicles at stage 16 or 17 have been published (Hanson et al. 1962, Figs. 3 and 8)[1].

Six auricular hillocks are characteristic: 1 (tragus), 2 and 3 (crus helicis), 4 and 5 (helix), and 6 (antitragus) (Streeter 1948).

The first pharyngeal cleft (hyomandibular groove) begins to form the concha and the external acoustic meatus (Streeter 1948).

Stage 18 (ca. 13–17 mm; ca. 44 days)

The precartilaginous otic capsule is in direct contact with the epithelial portions of the labyrinth (Streeter 1917, Fig. 4).

The semicircular ducts form from thickened epithelial areas. The adjacent epithelial layers fuse, lose their basement membrane, and disappear (O'Rahilly 1963, plate 2, Fig. K).

From 1 to 3 semicircular ducts are formed during this stage (Streeter 1948). The order is anterior, posterior, and lateral (Bast et al. 1947). The crus commune is evident from the beginning (Streeter 1906, plate 1, Fig. g).

The cochlear duct is L-shaped (Streeter 1951).

The bar of the first pharyngeal arch may begin to chondrify (Meckel's cartilage) (O'Rahilly and Gardner 1972). The bar of the second arch may chondrify also (Reichert's cartilage) (Personal observations)[2].

A reconstruction of the auditory ossicles has been published (Hanson et al. 1962; Fig. 11).

The stapes and stapedius can be identified (Personal observations).

The auricular hillocks are merging to form the primordia of definite parts of the auricle (Streeter 1948).

1 The reconstructions and photomicrographs illustrated by Hanson et al. (1962, Figs. 1–13) are of Carnegie embryos Nos. 617 (stage 16), 6524 (stage 18), 6517 and 559. Unfortunately, however, queries have been raised as to whether the last two belong to stage 16 or to stage 17

2 Hanson et al. (1962, Fig. 1) show the bars of the first and second arches at stage 16. These condensations, however, should be assumed to be merely blastemal at this early stage

Stage 19 (ca. 16–18 mm; ca. 48 days)

The otic capsule is cartilaginous but not yet connected to the basal plate (O'Rahilly and Müller 1983).

The tip of the cochlea becomes curled (Streeter 1951, Fig. 7).

The malleus and incus can be identified (Personal observations).

Stage 20 (ca. 18–22 mm; ca. 51 days)

The parietal lamina is present. The otic capsule is connected with the basal plate and with the future exoccipitals (O'Rahilly and Müller 1983).

The tip of the cochlea is elongated and curled (Streeter 1951, Fig. 7).

The tensor tympani and stapedius are visible in reconstructions (Blechschmidt 1963, plate 38).

Stage 21 (ca. 22–24 mm; ca 52 days)

The tip of the cochlea is recurved (Streeter 1951, Fig. 7).

Stage 22 (ca. 23–28 mm; ca. 54 days)

The cochlea continues its spiral growth (Streeter 1951).

Stage 23 (ca. 27–31 mm; ca. 57 days)

The otic capsule has been reconstructed and illustrated (Müller and O'Rahilly 1980, Fig. 5).

The cartilaginous otic capsule is separated from the semicircular ducts by a precartilaginous zone that is beginning to be excavated by dedifferentiation to form reticular tissue (Streeter 1917, Fig. 7).

The labyrinth "has practically completed its gross development" (Streeter 1906).

The ductus reuniens is well defined (Streeter 1906, plate 2).

The cochlea shows nearly $2^1/_2$ turns (Streeter 1951, Fig. 7).

Discussion

The Eye

Only staged embryos have been considered in this study and hence it has not been possible to include much otherwise valuable information (e.g., Wulle and Richter 1978; Rhodes 1978, 1979).

It has been found that the mesenchyme surrounding the avian embryonic eye is partly derived from neural crest. The crest cells, in addition to forming the frontonasal and maxillary processes, are believed to give rise to most of the connective tissues of the eye, including the sclera and choroid, as well as the stromal cells and posterior epithelium of the cornea, and the ciliary muscle (Johnston et al. 1979). To what extent these data would apply to the human is unknown. However, it has been shown in the human that a sheath of neural crest comes to envelop the optic vesicle and that this sheath receives contributions (the "optic neural crest") from the walls of the optic evagination (Bartelmez and Blount 1954; O'Rahilly 1966). It has been suggested that the optic neural crest develops into uveal pigment cells (Bartelmez and Blount 1954).

The Ear

Again, because only staged embryos have been considered here, it has not been possible to include much otherwise valuable information on the internal ear (e.g., Brunner 1934; Andersen et al. 1969), the middle ear (e.g., Schimert 1933; Candiollo and Levi 1969), and the external ear (e.g., Hochstetter 1948). A useful summary of the development of the ear has been published recently (Van De Water and Ruben 1976). In the bonnet monkey, staged data are available and have been summarized (Newman and Hendrickx 1981, Table 4).

Internal Ear. Epitheliomesenchymal interactions between the otic plate and the adjacent mesenchyme are "essential for orderly morphogenesis and histogenesis of sensory structures of the inner ear" (Van De Water et al. 1980). Moreover, the otocyst induces chondrogenesis in the surrounding mesenchyme.

The otic plate (in the mouse) becomes distinct because of thinning of the adjacent ectoderm rather than by actual thickening (Verwoerd et al. 1981). Moreover, the mesenchyme around the otocyst is believed to be derived, at least in part, from the neural crest (ibid.). Indeed, hypopigmentation may be associated with abnormalities of the internal ear in hereditary syndromes in several species, including the human (Deol 1970).

The endolymphatic duct (in the macaque) has been shown by autoradiography to grow at its base, so that the apical portion is pushed dorsally by repeated cellular division from below (Wilson et al. 1975).

Although in older studies the "acoustico-facial crest" was described as arising from the general neural crest ("from the fourth rhombomere", according to Bartelmez and Evans 1926), in more recent investigations the vestibulocochlear ganglion is generally thought to be derived from the otic vesicle (Politzer 1956), at least in part (Theiler 1949; O'Rahilly 1963). This conclusion applies in the human, pig, rabbit, cat, sheep, and chick, but in the mouse a contribution from the general neural crest has been proposed (Deol 1967).

Middle Ear. The possible developmental interrelationships between (1) the internal ear and (2) the middle and external ear are still uncertain. Moreover, the scanty data available concerning the development of the middle ear emphasize that "our ignorance of the morphogenesis of the middle and external ear far exceeds our knowledge" (Van De Water et al. 1980). Lack of data relating to the middle ear in staged human embryos is particularly evident.

The composition of the tubotympanic recess is still not entirely clear. In one study, for example, it was concluded that, between 10 mm and 20 mm, "there is a gradual reduction in the contributions from the second arch and second pouch to the tubotympanic recess so that the tympanum and tube are formed solely from the first pouch" (Kanagasuntheram 1967). In another investigation, however, "reservations concerning the concept that the middle ear derives from the first pharyngeal pouch" had been expressed (Goedbloed 1960). It had been maintained that the developing middle ear and the first pharyngeal pouch do not agree topographically and belong to different periods of development: "the period in which the first pharyngeal pouch disappears is exactly the period when the new extension in the oral cavity occurs which is to become the middle ear" (ibid. See also Goedbloed 1964).

The derivation of the auditory ossicles has not been entirely settled (Van De Water 1980, Fig. 19). In the human, the head of the malleus and the body and short crus of the incus develop from the first pharyngeal arch. The handle of the malleus, the long crus of the incus, and the head and crura of the stapes are believed to develop from the second pharyngeal arch (Anson et al. 1960, Fig. 11). The base of the stapes appears to arise in the lateral wall of the otic capsule (ibid. See also Hanson et al. 1962).

External Ear. The details of the formation of the auricle have long been disputed. The existence of the auricular hillocks of His has been confirmed (Aghemo and Fortunato 1969), although they may well be "of a transitory character and are incidental, rather than fundamental, to the development of the auricle" (Streeter 1922). According to Blechschmidt (1955), "there is neither a concrescence of the auricular hillocks ... nor a migration" of the auricle after its differentiation. It has been proposed that (in the rabbit) the entire auricle arises from the second pharyngeal arch, and that the tragus (which also develops from the second arch) migrates to the mandibular bar (Crary 1964).

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