J Am Acad Audiol 5: 359–365 (1994)

Development of Hearing. Part II. Embryology

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Abstract

We humans hear the way we do because of at least three major forces. The first is phylogeny, the evolutionary changes in the auditory system since its beginnings. Another is embryology, the development of the system in each individual. Finally, there is the biologically determined mechanism we are born with and our interaction with the environment in early postnatal life. This series of articles reviews each aspect so that we may have a fuller appreciation of how it is we come to hear the way we do. Part I described the phylogeny of the auditory system. Part II traces the development in prenatal life of the internal, middle, and external ear and the nervous system by days, weeks, and months. Wherever possible, parallels are drawn between phylogenetic and embryologic development. Part III considers the postnatal aspects of auditory development.

Key Words: Auditory pit, auditory placode, branchial arch, ear, ectoderm, embryology, endoderm, mesoderm, otic vesicle, otocyst

In the first of three articles in this series on the development of hearing, we reviewed development over time—the phylogeny—of the auditory system. The evolution of the ear was discussed against a backdrop of general evolution, from single cell life to humankind. We saw that the vertebrate auditory labyrinth evolved from the fishes' equilibrial labyrinth. Amphibians added the crucial middle ear for efficient air-conduction hearing on land. In reptiles, the auditory organ included a flexible, basilar membrane, a characteristic passed on to later-appearing classes. Eventually, the central auditory system reached its zenith in large-brained *Homo sapiens*. In this second part, we trace the embryology of the ear. In the concluding part, we examine the development of hearing in postnatal life.

The sequence of sensory system maturation somewhat mirrors that of sensory system appearance in vertebrates: tactile, vestibular, auditory, visual (Rubel, 1978). The focus here is on the auditory system. The embryology of the human ear has been described in detail elsewhere, and it is not the purpose of this article to repeat those discussions. Rather, the purpose is to make aural embryology both easier to understand and to remember. To help do so, the major steps in the embryology of the auditory system are depicted in Figure 1, week by week and month by month, beginning with January 1 and proceeding to term on September 23. That time span equals average human gestation of 266 days (reckoned from conception and not from last menstrual period), that is, 38 weeks or nearly 9 months. Development is related to prominent dates to facilitate recall. The principal parts of the ear are covered separately, but Figure 1 reminds us that the development of all parts is often simultaneous.

Inner Ear. If conception occurred on New Year's Day, then implantation of the embryo in the uterine wall would occur about January 8. The first sign of ear development is heralded around the end of the third week by a thickening of the outside layer of germ tissue, the *ectoderm*, on each side of the cephalic end. This aggregation of cells is the *auditory placode* (or otic placode), predestined to become the membraneous labyrinth. Promptly, the placode invaginates, that is, depresses inward to form the *auditory pit* (or otic pit). The pit soon closes upon itself in the fourth week around January 28 to form the *auditory vesicle* (or otic pit or otocyst) (Anson and Davies, 1980). These stages in the formation of the inner ear are diagrammed in Figure 2.

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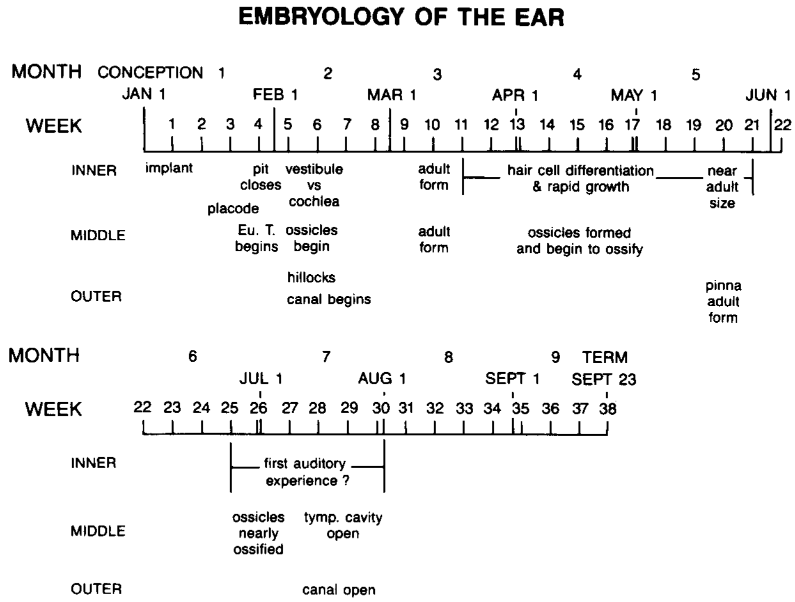

Figure 1 A time line highlighting major embryologic steps in the development of the ear for a normal gestation beginning January 1.

Hence, ectoderm, which gives rise to skin and the sense of touch, also supplies the germinal cells for the labyrinth and the sense of hearing. The phylogenetic association of taction and hearing was mentioned in the previous article and here we see the embryologic association between the two. However, since ectoderm also provides the basis for other tissues, such as the central nervous system, one ought not to exaggerate the relationship between feeling and hearing.

The otic vesicle migrates inward, and, as was the order phylogenetically, the vestibular portion takes shape slightly before the cochlear (Carlson, 1988). By the end of 5 weeks, the vestibular and cochlear divisions of the labyrinth are discernible (Kenna, 1990), and by February 14, Valentine's Day, the anterior aspect is elongating as the start of the cochlea.

So swift is the growth of the labyrinth that by week 10, the cochlea attains nearly adult form (Kenna, 1990). This amounts to two-and-a-half turns in about 2 ½ months (refer to Fig. 3).

To allow such rapid expansion, the *mesodermal* tissue environment (middle embryonic germ layer) is cartilaginous but is gradually turning to bone. By 8 weeks, the embryo passes a major milestone and becomes a fetus with unequivocal human characteristics.

Differentiation of the organ of Corti begins in the 10th week (Anson and Davies, 1980). First, around St. Patrick's Day (March 17),

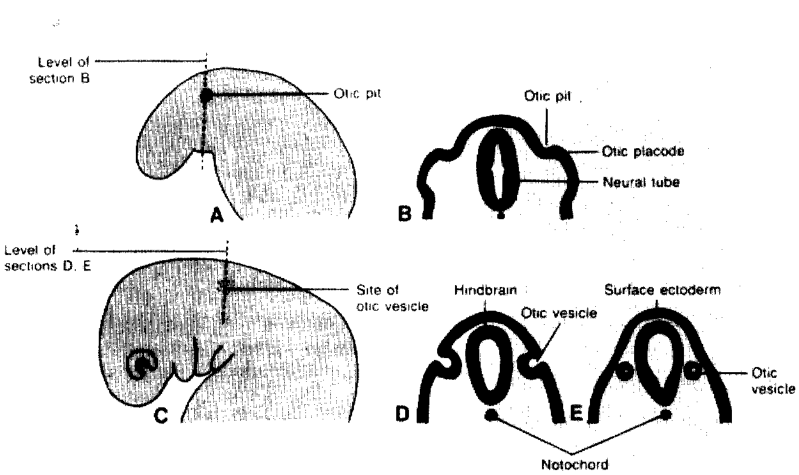

Figure 2 A schematic diagram illustrating the steps in the formation of the otic vesicle or otocyst. *A*, Lateral view of cephalic end of embryo at age 24 days; note otic pit showing the location of the otic placode. *B*, Transverse section at same age as *A*, showing the otic placode starting to invaginate to form the otic pit. *C*, Lateral view at age 28 days, with the otic pit nearly closed off from the surface. *D* and *E*, Transverse sections at same age as *C*. Note in *D* that the pit has nearly closed over on itself and in *E* closure is complete, forming the otic vesicle. (Adapted with permission from Moore, 1988.)

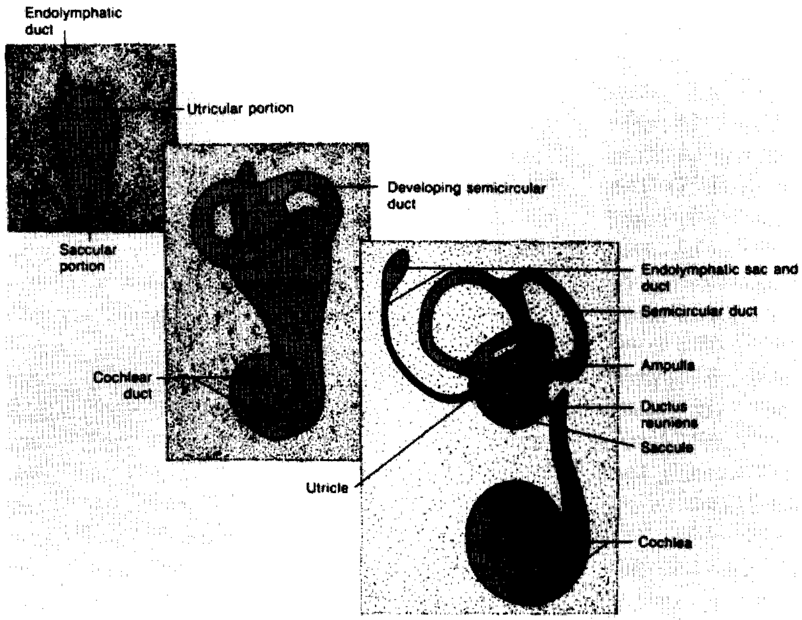

Figure 3 A schematic diagram illustrating stages in the formation of the membraneous labyrinth. Left, auditory vesicle elongating soon after being closed off from surface; note vestibular portion in advance of saccular portion, from which cochlea arises. Middle, semicircular canals and cochlear coils developing at 7 weeks of age. Right, all landmarks of membraneous labyrinth well formed at age 8 weeks. (Adapted with permission from Moore, 1988.)

there is a thickening of epithelium in the cochlear duct. From the third to the fifth month, this thickening differentiates into the distinct receptor and support cells of the organ of Corti (see Fig. 4).

The gradient of cochlear hair cell maturation is base to apex. Although development is primarily toward the apical end, it is also bidirectional, that is, it begins near the middle of the basal turn and proceeds in each direction (Rubel, 1978). Maturation of the base leads that of the apex by 1 or 2 weeks (Lavigne-Rebillard and Pujol, 1988).

Cochlear development presents a paradox. In mature cochleas, the apical end is maximally responsive to low frequencies and the basal end is maximally responsive to high frequencies. However, in developing cochleas, responsiveness to low and middle frequencies precedes responsiveness to high frequencies. This would suggest that the apical turn should mature first and the basal turn last. But the case is actually the reverse. As noted above, maturation of the organ of Corti proceeds generally from base to apex. The solution to this paradox is that during the period of functional maturation, the mechanics of the inner ear change, so that the basally located cells initially respond to relatively low frequencies and then, as the organism matures, respond optimally to ever higher frequencies (Rubel et al, 1984; Rubel, 1985).

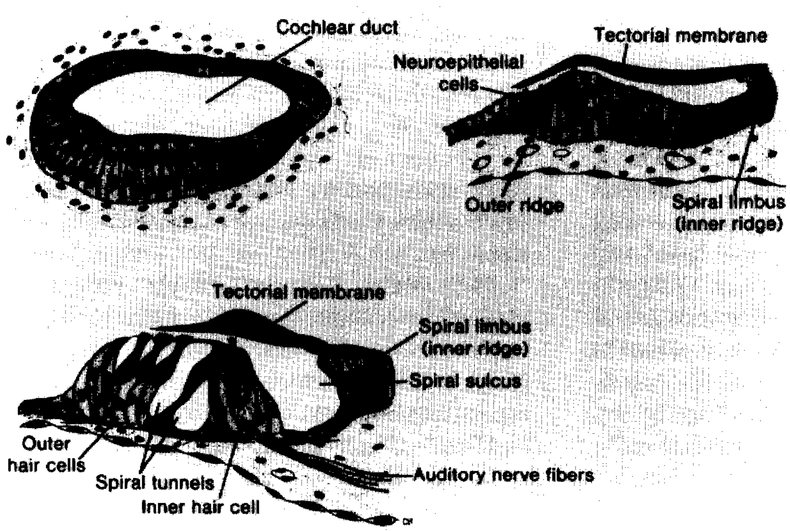

Figure 4 Illustration of stages leading to the organ of Corti. Top left at 10 weeks; top right at approximately 5 months; bottom at full term. (Adapted with permission from Sadler, 1990.)

There is a second gradient of cochlear receptor cell development: internal to external. The inner hair cells (IHCs) appear slightly earlier than the outer hair cells (OHCs) at the same location along the basilar membrane (Patten, 1968; Lavigne-Rebillard and Pujol, 1988). The "older, more primitive" inner hair cells seem less susceptible to various noxious influences, such as age, trauma, or pathogens. Whether or how the time sequence makes the IHCs more resistant is uncertain (Rubel, 1978). The labyrinth, meanwhile, continues to expand rapidly, so that near the end of the fifth month, it is close to adult size. Thus, the cochlea is full sized and basically equipped in a span of 6 months, the time from New Year's to Memorial Day.

Nervous System. The development of the VIIIth nerve and of the central auditory system is equally important but less understood. Ganglion cells from the VIIIth nerve arise from the otic vesicle in the fourth gestational week. VIIIth nerve fibers start to enter the expanding cochlea in the fifth week (see Rubel, 1978). Afterwards, the cochlear branch of the VIIIth nerve fans out in synchrony with the curving cochlea. Synaptic connections follow the same sequence as that of hair cell development, that is, contacts with the IHCs are in advance of contacts with the OHCs. Radial dendrites make contact with IHCs in weeks 11 and 12, whereas spiral fibers contact the base of the OHCs in week 14. Efferent innervation is generally later than afferent innervation with axonic connections occurring between weeks 15 and 22 (Pujol and Lavigne-Rebillard, 1985). All synapses are formed by the seventh fetal month, and final steps in maturation of contact between the cochlea and peripheral nerves take place in the last trimester (Lavigne-Rebillard and Pujol, 1988).

As we have seen, the organ of Corti is well formed in the fifth month and synapses are forming in months 4 to 6. When, then, does the cochleo-neural mechanism begin to function? A whole list of mechanical and neural conditions must be met: (1) connections between the apex of hair cells and the tectorial membrane; (2) adequate internal structure of hair cells; (3) mature synapses between base of hair cells and nerve fibers; (4) maturity of ganglion cells; (5) thinning of the basilar membrane; (6) degeneration of pseudostratified epithelium of the inner spiral sulcus; (7) maturity of pillar cells; (8) freeing of the inferior margin of the tectorial membrane from the organ of Corti; and (9) forming of spaces in the tunnel of Corti and around the OHCs (Rubel, 1985; Romand et al, 1987). Romand et al (1987) consider the first most important. Pujol and Lavigne-Rebillard (1985) agree that the crucial step is the juncture of the stereocilia, cuticular plate, and tectorial membrane. The precise time of onset of function is still speculative, but it could be that the sensorineural system is sufficiently mature to permit experiencing the sensation of sound near the end of the sixth or start of the seventh month (early July).

As for the central auditory system, Heschel's gyrus begins to form in the cortex at around 2 months. Primary central pathways are in place and functional long before the onset of cochlear function (Rubel, 1978). By 7 months, the cortex may have all its cells and all six layers. Myelination of the projection fibers from the thalamus is sparse at birth and progresses to 4 years of age. Intracranial fibers undergo myelination into adolescence.

It must be kept in mind that normal growth of central auditory neural elements requires an intact peripheral mechanism, at least according to animal studies (Rubel, 1985). This is an example of structures developing in different sites mutually influencing one another. Auditory structures in the brain stem initially develop independently, but their full destiny cannot be attained without afferent stimulation (Rubel, 1985).

Middle Ear. The origin of the middle ear is first in evidence during the fourth week (Ars, 1989). The first *pharyngeal pouch* extends lateralward to form the *tubotympanic recess*, the primordium of the eustachian tube and the tympanic cavity. This is in contrast to the inner ear and shows the remarkable difference in directions taken by parts of the developing ear. Whereas the inner ear migrates from outside inward (invagination of the ectodermal auditory placode), the middle ear develops from inside outward (evagination of the endodermal pharyngeal pouch). The right-hand side of Figure 5 shows the sequence of middle ear formation.

In weeks 5 and 6 (early February), *mesenchymal* cells lying between the embryonic inner ear and the first *branchial groove* (or furrow) on the surface begin to show areas of concentration, areas destined to become the ossicles. At nearly the same time, that same first branchial groove widens to foreshadow its inward extension to become the external auditory meatus. (The branchial or gill structures

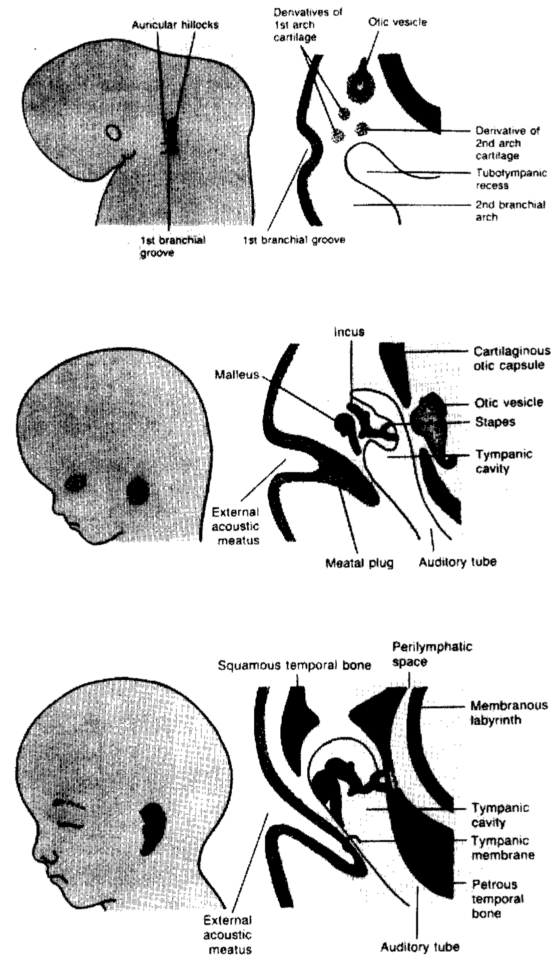

Figure 5 Schematic drawings showing the development of the outer and middle ears at three different stages of embryonic development: 4, 10, and 32 weeks. The left side shows lateral views of head, and the right side has corresponding frontal sections through the middle ear region. The auricle develops from the hillocks around the first branchial groove. The external auditory meatus originates as the first branchial groove. The ossicles begin as areas of mesenchymal condensation to become well-formed bones. The auditory or Eustachian tube and middle ear cavity result from expansion of the tubotympanic recess, eventually creating an open space for the ossicles. (Adapted with permission from Moore, 1988.)

are an embryologic holdover from our vertebrate ancestry back to fish.) The head and neck of the malleus and the body of the incus are derived from the first branchial arch, whereas the handle of the malleus, the long process of the incus, and the superstructure of the stapes derive from the second branchial arch. The footplate has a double parentage, the lateral surface from the second arch and the medial surface from the otic capsule (Ars, 1989; Kenna, 1990). The ossicles form quickly and have their recognizable landmarks by about the 10th week (mid March). According to Ars (1989), ossification begins about the time when the ossicles attain nearly adult size and shape, namely, the 15th week (Anson and Davies, 1980) (i.e., by about the time income tax is due, April 15). By 26 weeks, the malleus and incus are ossified except for the extreme distal end of the malleolar handle, which is often hypoplastic or absent in congenital aural atresia (Ars, 1989). The stapes continues to develop into adulthood, assuming a more delicate architecture. As for their muscle attachments, the tensor tympani derives from arch I and the stapedius muscle from arch II in that order (Kenna, 1990).

For much of their developmental time, the ossicles are surrounded by mesenchymal tissue and not contained in a middle ear space. During months 3 to 7, this tissue resorbs, resulting in a marked expansion of the tympanic space to provide a housing for the ossicles. Thus, even though the ossicles are mostly formed by 4 months, they are not enclosed in an open tympanic cavity until the seventh month or mid July (refer once again to the right side of Fig. 5). At birth, there may be some remaining tissue and fluid in the tympanum, which are quickly replaced by air.

Outer Ear. Just as the outer ear was the last part of the ear to appear phylogenetically, it is the last part to begin forming embryologically. Around the fifth week (early February), changes occur in the ridges and furrows of the vestigial gills on each side of the head. Branchial groove I begins widening as start of the external auditory canal. Curiously, the primitive outer ear and middle ear are in brief contact at the tympanic membrane only to lose contact again in the next 5 months. That is, in the fourth to fifth week, ectoderm of the first branchial groove contacts *endoderm* (internal embryonic germ layer) of the first pharyngeal pouch to form a prototympanic membrane. Then, mesoderm intervenes for several months (Kenna, 1990). Around this opening, six tissue thickenings, called *hillocks*, arise from the branchial arches I and II. There is uncertainty about what parts of the pinna derive from which arch. One view holds that these "little hills" evolve into the tragus from arch I and into the rest of the auricle from arch II. A more common view is that the anterior third of the auricle is from arch I and the rest is from arch II. The pinna is well formed by day 37 (Anson and Davies, 1980). It will be 4 ½ months (mid May) before the pinna has essentially adult form (Kenna, 1990), although it

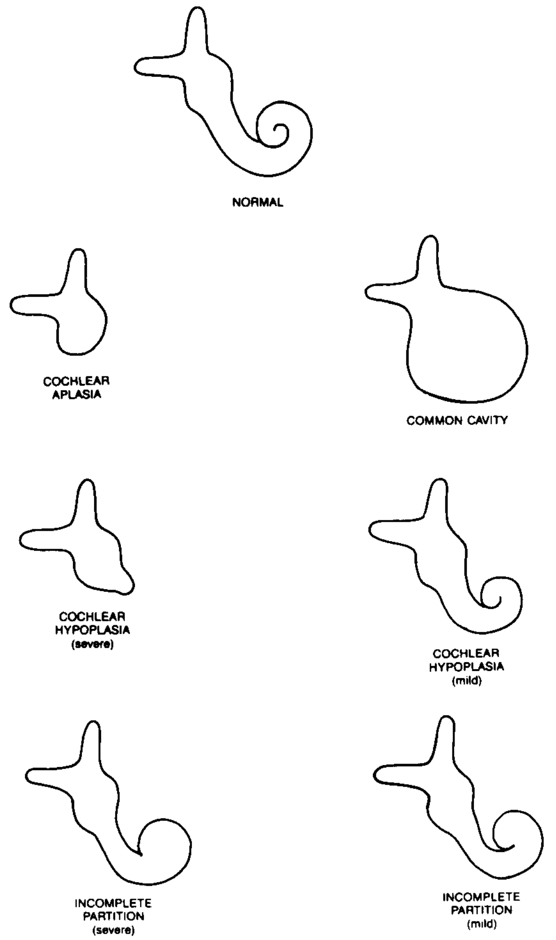

Figure 6 An embryologic model of inner ear malformations, the severity of which is determined by the time of insult. The earlier the insult, the more extensive the malformation. (Adapted with permission from Jackler et al, 1987.)

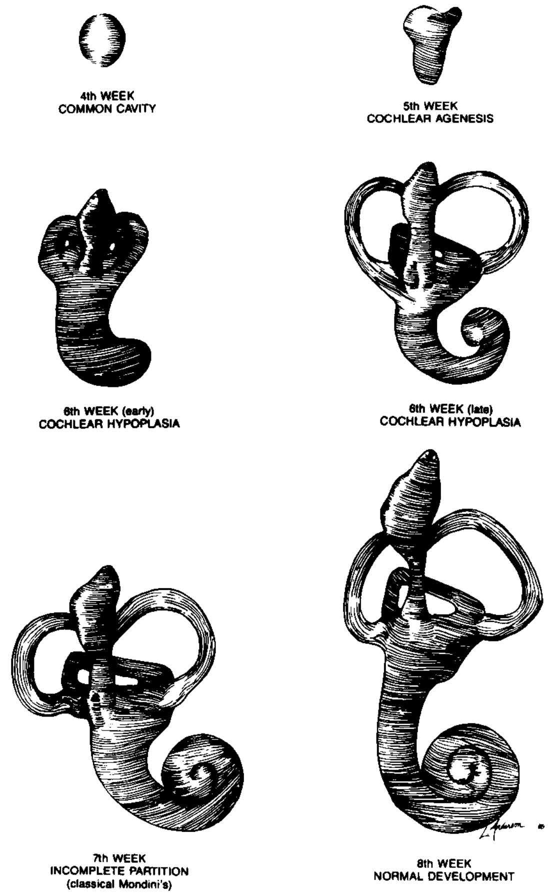

Figure 7 Illustrations of a normally developing labyrinth and the names of the malformations associated with the time of arrest in development. (Adapted with permission from Jackler et al, 1987.)

continues to grow until age 9 years, and even then there are changes into senescence. The formation of the pinna is schematized in the left-hand portion of Figure 5.

The tympanic membrane, although surrounded by mesoderm, trebles its diameter during weeks 11 to 16 (late March to late April), and its shape is completed by week 19 (mid May) (Ars, 1989). The membrane begins nearly horizontal (inferior portion into the middle ear region) and steadily approaches (but never attains) vertical. Tissue is progressively absorbed, from the tympanic space medially and from the branchial groove laterally, until the end of the seventh month or 28 to 30 weeks, when the external canal is essentially open and only the tympanic membrane remains (see once again the right-hand panel of Fig. 5). The membrane manifests its triple origins: on the inside, a mucosal layer from endoderm; on the outside, skin from ectoderm; and, "sandwiched" in between, an elastic, fibrous layer from mesoderm. Its destined degree of verticality and curvature are reached by age 3 years (Ars, 1989).

Disorders. The embryology of the ear has implications for certain ear disorders. Since all three parts arise from different embryonal tissues, a disorder in one part of the ear does not necessarily signify a disorder in another. On the other hand, since these tissues are in such close proximity, multiple ear malformations are quite possible. Because of their more similar origins from the region of branchial arches I and II, outer and middle ear disorders are far more likely to coexist than are outer or middle ear disorders with inner ear disorders. Still, Valvassori et al (1969) found a "striking association" between anomalies of the inner and middle ears. In their series, 25 percent of the ears with inner ear anomalies also had a middle ear disturbance on the same side. Conversely, 22 percent of Phelps' (1974) patients with external and middle ear anomalies had an inner ear deformity, albeit mostly of the semicircular canals. Along the same line, 47 percent of Potter's (1969) aural atresia cases had concomitant inner ear abnormalities, primarily of the oval and round windows and the semicircular canals.

The timing of insults to the developing fetus greatly influences the extent of the disorder. The earlier the disturbance, the more extensive the anomaly. Depending on where they impact, insults in the first fetal month would result in only a rudimentary external, middle, or inner ear. In contrast, insults after the sixth month have little effect on these structures.

Jackler et al (1987) classify inner ear malformations based on just such embryologic considerations. Their schema helps explain conditions of arrested development (as opposed to aberrant development, which also produces various abnormalities). Figure 6 outlines the range of malformations from very severe to rather mild, depending on the time of occurrence. For comparison, Figure 7 illustrates what the labyrinthine structures should look like at corresponding times in early development. Note that the span of time is a mere month.

In general, the greater the abnormality, the greater the hearing loss (Jackler et al, 1987). Here is the sequence of malformations that, according to Jackler et al (1987), would result from an arrest in maturation at different times during early pregnancy: 3rd week: complete labyrinthine aplasia ("Michel" deformity); 4th week: undifferentiated labyrinth or common cavity; 5th week: cochlear agenesis; early delineation of the semicircular canals, vestibule, endolymphatic sac, and cochlea, but the cochlea is completely undeveloped or aplastic; 6th week: cochlear hypoplasia, severe to mild, depending on early or late in the 6th week; 7th week: only 1–1½ turns with incomplete partition between the cochlear scalae ("Mondini" deformity).

This discussion of ear embryology concludes Part II of the development of hearing. In the final part, we treat the development of hearing in postnatal life to the time of onset of speech at age 12 months.

Acknowledgment. I am grateful to Drs. David Lipscomb, Noel D. Matkin, Edwin W. Rubel, and Robert Oyler for their editorial help in preparing this series of papers. Particular appreciation is extended to L. Judson Farmer, friend and colleague, who suggested I undertake this project and urged its completion.

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