Comprehensive Handbook of Pediatric Audiology

Second Edition

Anne Marie Tharpe, PhD
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Foreword

It is difficult to pinpoint when the term *pediatric audiology* actually came into common usage. We can only assume that the concept of pediatric audiology began shortly after the development of the discipline of audiology during and following World War II. We do know that Canfield, an otolaryngologist from Yale University, made one of the earliest references to pediatric audiology in his seminal book *Audiology, The Science of Hearing* (1949). However, long before the 1940s, historical writings clearly show that early civilization experienced and appreciated the problems associated with deafness in childhood. Indeed, Greek and Latin writers referenced the plight of the deaf on several occasions in the Bible.

During the Renaissance through to the latter part of the 19th century, we read about teachers and priests who were dedicated to serving children with hearing loss. This was a period in deaf education sometimes referred to as "the age of teaching"; it was an era in which the oral method clashed with teachings that emphasized the use of signs and finger spelling. Such well-recognized teachers as Pedro Ponce de León and Juan Pablo Bonet of Spain, Samuel Heinicke of Germany, Abbe Charles Michel de l'Epee of France, and Thomas Braidwood of Scotland were early pioneers of methods and techniques for educating young deaf children. One well-known scholar who brought specific teaching methods and philosophies from Europe to America was Thomas Gallaudet. After studying with de L'Epee in Paris, Gallaudet returned to the United States and established the first school for deaf children in Hartford, Connecticut, in 1817. The school was called the American Asylum for the Education and Instruction of the Deaf and Dumb.

During the early 20th century, pediatric audiology was not yet a recognized specialty, but educational and health care professionals throughout the United States became involved by necessity in the identification, assessment, and management of very young children with hearing loss. Perhaps most notable was the work of Sir Alexander and Lady Irene Ewing who worked tirelessly to serve young children with hearing loss in Great Britain. As early as 1919, Irene Ewing opened a hearing clinic at Manchester University. The Ewings, more than anyone during this period, influenced professionals throughout the world on issues pertaining to the identification and management of childhood deafness. They introduced some of the fundamental concepts now associated with pediatric audiology: the benefits of early identification and intervention including hearing aids, the importance of parent-home training for the development of speech and language, and the effective approaches for testing young children with hearing loss. By most accounts, this was the beginning of pediatric audiology.

By the late 1950s and early 1960s, a small group of audiologists was beginning to focus its efforts on young children, and we began to hear the term *pediatric audiology* on a more frequent basis; soon thereafter, training programs started to offer specialty tracks in pediatric audiology. There were few books dedicated to young children with hearing loss. As there was no single text that met the specific needs of pediatric audiologists or university training programs, several resource books were considered essential reading. These books included *Educational Guidance and the Deaf Child* (Ewing, 1957), and *New Opportunities for Deaf Children* by Sir Alexander Ewing (1959); *Auditory Disorders in Children* by Myklebust (1954); *Deafness in Childhood* by McConnell and Ward (1967); and *Hearing and Deafness* by Davis and Silverman (1960).

Clinical protocols related to identification, assessment, and hearing aid fitting for very young children also was limited. Evidence-based procedures had not yet been developed, and clinicians working with children were forced to rely mostly on intuition and common sense for their clinical decision making—clinical practice was probably more art than science. As Liden and Harford (1985) observed, pediatric audiologists "waved their magic wand and sprinkled whiffle dust to make the child's invisible reactions visible" (p. 6). Importantly, robust clinical tools commonly used today, such as electroacoustic immittance measures, auditory brainstem responses, and otoacoustic emissions, were not yet available to pediatric audiologists for the identification, assessment, and management of children with hearing loss. Although the profession of audiology recognized the importance of early identification of hearing loss in children, the average age of identification in the United States was 3 to 4 years, and there was a significant lag between the age when a child was identified and the age when a child actually received a hearing aid. Hearing aids were large, unattractive, and produced a great deal of distortion. Receiver buttons were used to modify the electroacoustic responses of hearing aids, and Y-cords served to provide a child with bilateral amplification. Hearing aid fitting was accomplished using a comparative approach for aided sound-field behavioral thresholds. The hearing aid that provided the most threshold improvement with the least amount of irregularity across frequencies was thought to provide the best speech understanding and subsequently was the hearing aid of choice. Because it was difficult to obtain accurate thresholds on young children using behavioral methodology, the fitting strategy was an ongoing process sometimes taking more than a year to finalize.

The contents of this new edition (second) of *Comprehensive Handbook of Pediatric Audiology*, serve as a stunning reminder of how far we have come since those early years in our efforts to serve young children with hearing loss and their families. Indeed, one cannot help but be impressed with the many positive changes that have occurred since the first edition of this book. Today, better graduate education, advanced technology, and innovative clinical research have brought about significant improvements in early identification of hearing loss, audiological assessment, the selection and evaluation of amplification, and the management strategies used with young deaf children. We now have the ability to identify hearing loss in the vast majority of newborns, obtain reliable frequency-specific threshold information on infants and toddlers, and objectively fit young babies with digital hearing aids and other assistive devices. The advent of cochlear implantation has resulted in significant improvements in the speech, language, and listening skills of children with severe-to-profound bilateral sensorineural hearing loss. We also have witnessed improvements in technology and medical care that have brought about changes in the prevalence of causation and severity of hearing loss. The second edition of *Comprehensive Handbook of Pediatric Audiology* addresses all of the relevant issues impacting today's young children with hearing loss and their families. It is exciting to see in one volume comprehensive coverage of contemporary trends in pediatric audiology. No doubt, the information contained within this new edition will be of value to those who seek to better understand the perplexities of childhood deafness and motivate others to search for newer and better ways to serve young children with deafness.

A portion of the proceeds from this book will be dedicated to a student scholarship fund at Vanderbilt University named in memory of Judith S. Gravel, an outstanding alumna of Vanderbilt University and one of the true giants of pediatric audiology. In fact, it was Judy Gravel who originally envisioned the need for a book in audiology that focused on pediatric hearing loss. Her presence can be seen throughout the entirety of this book simply by reviewing the references at the end of each chapter that highlight her diversity of interest areas and contributions to the profession. Although Judy was taken from us at a young age, her life was filled with love, fun, and accomplishments that far exceeded her years. To be sure, we are all so very fortunate that she shared her many gifts with us.

—Fred H. Bess, PhD

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The concept and original outline for this book were developed at a meeting with Dr. Judith Gravel in July 2006. Judy was a big dreamer and saw a great need for a comprehensive text in the area of pediatric audiology. With a twinkle in her eye, she referred to this book as "the mothership." By the end of this meeting, the Table of Contents included chapters covering every conceivable topic related to the basic sciences, screening, assessment, and management associated with childhood hearing and hearing loss. It was her vision and passion that led to the development of this book. Two weeks following the July 2006 meeting with Judy, she was diagnosed with cancer. We lost Judy on December 31, 2008. Throughout her courageous battle with cancer, we asked Judy on numerous occasions if she wanted to continue the work on the book. Our queries were always greeted with silence. When Judy became silent the answer was always clear. To discontinue work on this project was never an option for Judy. We have done all that we could to ensure this book lives up to Judy's dream. We thank you, Judy.

It is possible that our work on this book had more missed deadlines than the book has pages. Nonetheless, throughout this journey we have always had the support, expertise, and patience of the exceptional group at Plural Publishing. Specifically, we would like to thank Angie Singh for her genuine encouragement and support from the very start. Throughout the process, Valerie Johns, Kalie Koscielak, and Nicole Bowman have always been there to nudge us along gently and to help us with even the smallest editorial detail. We cannot imagine having a more positive and informed group with whom to work.

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Finally, we would like to thank our life partners Jim and Carol for their unqualified support of our work on this project—we promise to make up for lost time!

—Anne Marie Tharpe and Richard Seewald

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This book is dedicated to our dear friend and colleague Judith S. Gravel, whose vision for this volume guided our every step. Judy was beautifully unique. She was a scholar, a scientist, a teacher, and a master clinician whose career exemplified the highest standards of professionalism and ethical conduct. Above all, she was a warm and caring person with a remarkable way of bringing out the best in everyone whose life she touched, including children whom she loved the most.

Dr. Judith S. Gravel
December 1948–December 2008

1

Hearing Development: Embryology of the Ear

Mark Hill

Developmental Origins

Human embryology at the turn of the last century identified selected aspects of ear structural development as part of the overall study of the development of the head and nervous system in studies by Thyng (1914). Studies of animal models played an important role in the early history of auditory embryology. For example, as early as 1911, Jenkinson examined the embryological development of the middle ear in mice. Studies of embryonic human external ears followed in the 1930s (Wood-Jones & Wen, 1934). The chicken model was also used around this time for studying the development of the central auditory pathway (Levi-Montalcini, 1949). In the 1940s and 1950s, research focused on the relationship between the human auditory system and the general embryonic stages of development (Streeter, 1942, 1948, 1951). It was not until the 1950s that hearing development research took off with many studies on embryological, anatomic, and neurologic development. Today, a search of the PubMed reference abstract database with "development of hearing" will return more than 10,000 studies. The current studies mainly utilize animal models and study the molecular mechanisms of development. In particular, genetic and teratological studies have and are identifying a growing number of specific genes and teratogens associated with auditory abnormal embryology. Our current understanding of developmental mechanisms and gene function has led to potential future treatment of genetic deafness through gene therapy (Askew et al., 2015).

This chapter introduces the embryology time course of the human ear as divided by the three anatomic divisions (Figure 1–1, external, middle, and inner). The description also draws on the many animal model studies that have helped us further understand human auditory development. Examples are given of embryologic studies currently unraveling the complex signaling pathways involved in development. Many of these pathways involve a regulated sequence of secreted growth factors, transcription factor "switches," gap junctions, and adhesive interactions choreographed into a back-and-forth signaling process between developing ear structures and surrounding tissues. Finally, a brief overview of critical periods of embryologic development in relationship to genetic and environment conditions is given. Note that neurologic and postnatal development is covered elsewhere in this text (see Chapters 2 and 4) and in recent reviews (Fritzsch, Knipper, & Friauf, 2015; Litovsky, 2015). Human embryology stages and the organ of audition and equilibrium are also described in the online resource Embryology (http://tiny.cc/Hearing_Development).

General Human Embryology

When staging human prenatal development, there is an important consideration and sometimes confusion when reading the literature. Embryologists consider fertilization to initiate development and all following staging commences from this point in time. Clinicians, other than with in vitro fertilization (IVF), cannot easily ascertain the time of fertilization. In this case, a far easier and more predictable timing is from when the mother is not pregnant, that is, the last menstrual period (LMP). Therefore, there is often approximately a 2-week difference, as fertilization occurs after ovulation at the midpoint of the menstrual cycle. For example,

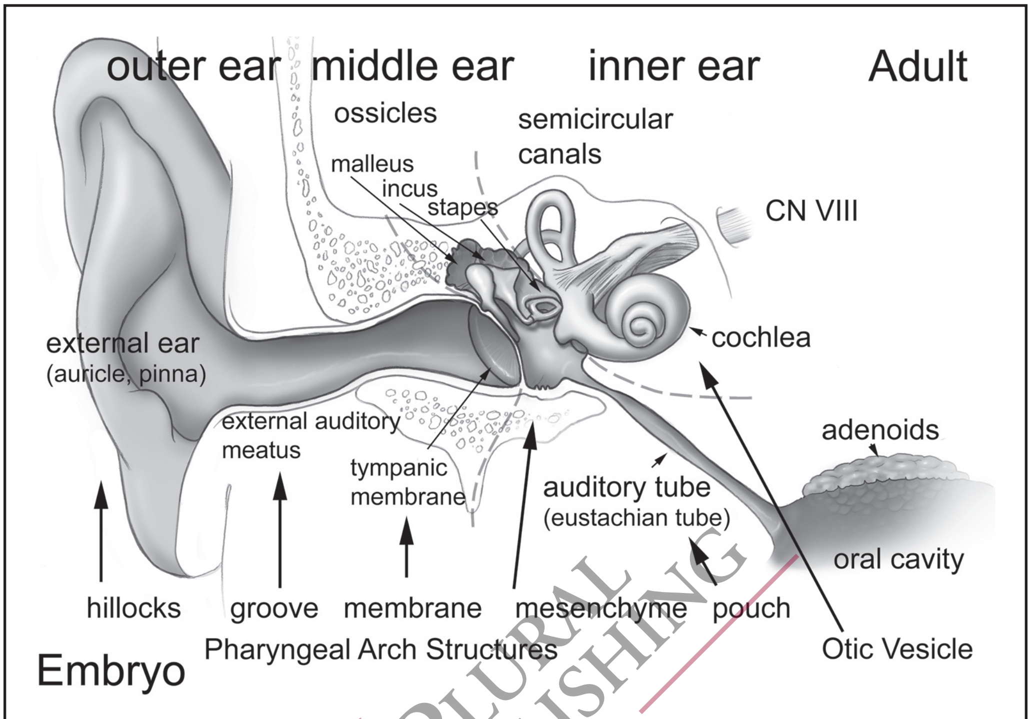

FIGURE 1–1. General anatomy of the adult ear and the equivalent embryonic structures from which each component is derived. The inner ear forms from the surface otic placode forming the otic vesicle (or otocyst), which contributes the membranous labyrinth and cranial ganglia. The middle and external ear form from components from pharyngeal Arch 1 and 2. (Image based on NIH imagebank and National Institute on Deafness and Other Communication Disorders [NIDCD].)

postfertilization Week 3 is clinically Week 5 LMP. All timings described in this current chapter refer to embryologic dates from fertilization.

In the first 3 weeks of development, the embryo forms initially as three main layers (trilaminar), or germ layers, from which all tissues of the embryo derive. These three layers are the ectoderm (forms all neural tissue and the surface epithelium); the mesoderm (forms most connective tissues of the body; muscle, bone, cartilage); the endoderm (forms the lining epithelium of the gastrointestinal, urogenital, and respiratory tract). Each of these layers begins as a simple circular disk of cells stacked like dinner plates. The three layers later will segment themselves into different regions, which contribute to specific tissues. Specialized senses such as hearing and vision will have contributions from all three of these embryonic germ layers during their complex developmental process.

In the fourth week of development, organogenesis begins throughout the embryo, which converts the trilaminar embryo into anatomically identifiable organs and tissues. In humans, the first 8 weeks of development are described as the embryonic period when organogenesis occurs. This is followed by the fetal period when continued growth and differentiation of mainly preexisting tissues and organs occurs. Classically, the embryonic period has been divided into 23 Carnegie stages, describing development as a series of observable changes in external appearance and features of the embryo. Stage 1 begins at fertilization, Stage 7 at implantation at the end of the first week, and Stage 23 the end of the embryonic period in the eighth week. The same classification can be applied to embryos of many different species, allowing direct developmental comparisons although over different time periods for each species stage. This classification has also been useful for studying the embryological development of human hearing and balance using a variety of animal models (mainly chicken, mouse, rat, and zebrafish), which will be referred to within this chapter.

Normal embryonic system development, including hearing, requires a combination of developmental signaling mechanisms. These mechanisms include short- and long-distance interactions by secretions (growth factors, hormones, and ionic changes), adhesive interactions (cell-cell, cell-extracellular matrix), and a subsequent cascade of transcription factors (DNA binding proteins). These transcription factors activate key genes required at specific developmental stages and eventually the adult pattern of gene expression in that cell or tissue.

Clinically, the embryonic period can also be seen to occupy most of the first trimester, and the fetal period occupies the second and third trimester of human development. This division of development is also an important consideration when we look at the critical periods of development that can be impacted by teratogens. This chapter includes brief coverage of some molecular regulatory mechanisms of normal development, as perturbations of these signaling pathways relate to abnormalities of hearing and balance. The following sections cover initially the early embryonic development of all three anatomic ear divisions, which are followed by later fetal development and detailed development of the cochlear and key auditory components.

Early Inner Ear

The earliest external feature of auditory development is the appearance on the ectoderm of the embryo surface in the head region of otic placodes (for a review, see Whitfield, 2015). These placodes form as a pair of the series of placodal regions that form initially at the edge of the neural plate. The otic placodes are two small circular regions of ectoderm on the lateral surface of the developing head and the first "visible" pair of sensory placodes that eventually will contribute to each sensory system (hearing, vision, smell, and taste). In other species, there can be additional sensory placodes that contribute to sensory systems not present in humans. The otic placode lies closely associated with, but separate from, the neural tube level that corresponds to the hindbrain region of the neural tube. This localization with the neural tube later can be further positioned as adjacent to rhombomere 5 and 6 segmental subdivisions of the hindbrain.

The otic placode is a single layer of ectodermal cells organized in a columnar epithelium, which differs in cell shape from the surrounding cuboidal epithelia that will contribute the epithelia of the skin. In the zebrafish model, a number of specific genes are involved in initial induction of the otic placode including both growth factors (FGF3 and FGF8) and transcription factors (dlx3b, dlx4b, and foxi1; Solomon, Kwak, & Fritz, 2004).

Proliferation of the otic placode cells leads to an inward folding, or invagination, giving the external appearance of a depression on the lateral sides of the early developing neck region. The epithelium is still a single layer of cells, which continues to invaginate until the edges of the disc of cells come into apposition on the embryo surface. In the mouse model, placodal invagination but not specification requires placodal expression of the transcription factor Sox9 (Barrionuevo et al., 2008).

Further invagination leads to the edges of the placode coming into close apposition and then fusing to form a hollow, fluid-filled sac; this structure is then renamed as the *otic vesicle* or *otocyst* (Figure 1–2). The otic vesicle is the primordium of all the inner ear structures, including the cochleovestibular neurons of the future cranial nerve eight (CN VIII). The otic vesicle is now lost from the embryo surface and sits embedded within the mesenchyme, embryonic connective tissue, behind the first and second pharyngeal arches. The otic vesicle is surrounded by a number of developmental structures including the fifth rhombomere (medially), the anterior cardinal vein (laterally), and developing cranial ganglia (rostro-caudally). These events of otic placode formation, invagination, and otic vesicle formation all occur within the third week of human development.

Otic Vesicle Development

The inner ear membranous labyrinth has two major linked components, the vestibular system (semicircular canals) and the auditory system (cochlea duct). Both are derived from the otic vesicle. This section will detail the early events of otic vesicle differentiation followed by specific notes on the later development of both systems.

By the fourth week, the otic vesicle is a spherical epithelial fluid-filled ball at the level of rhombomere 5 and 6 (Hatch, Noyes, Wang, Wright, & Mansour, 2007). During this week, neuroblasts delaminate to form the primordial of the vestibulocochlear (statoacoustic) ganglion, the vesicle elongates, and the walls also change in relative thickness. This initial elongated portion of the otic vesicle will form the endolymphatic sac.

The beginning of otic vesicle differentiation is the localized expression of transforming growth factor-β2 (Okano et al., 2005). The site (see Figure 1–2) of this expression in the otic wall locates cells that will delaminate and contribute to formation of the statoacoustic

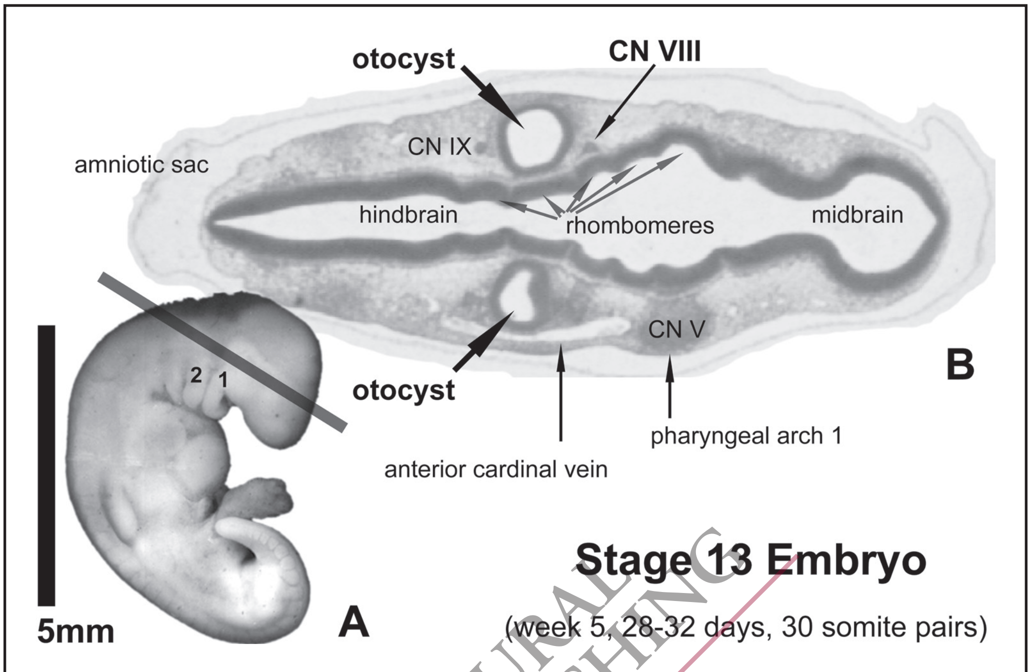

FIGURE 1–2. Stage 13 embryo (Week 5) showing otocyst that will form the inner ear. **A.** Ventrolateral view of the whole embryo with 5-mm scale bar. At this stage of development, no middle or external ear structures are apparent and will be derived later from pharyngeal arches 1 and 2 (*labeled*). **B.** The gray bar through the head indicates the plane of cross section, which is a cross section of the head showing the size and position of the otic vesicles. At this stage of development, the vesicles lie within the head mesenchyme behind pharyngeal Arch 1 and 2 and in close apposition to the developing hindbrain. Note the close position of the otic vesicle to the rhombomeres, hindbrain folds that represent the initial segmentation of the hindbrain. Also shown are developing cranial ganglia and blood vessel lying adjacent to the otic vesicles. The wall of the otic vesicle at this stage is a simple epithelium.

ganglion or cranial nerve CN VIII (Andermann, Ungos, & Raible, 2002; Represa, Moro, Gato, Pastor, & Barbosa, 1990). These cells remain adjacent to the otic vesicle residing in the surrounding cellular mesenchyme, a mixture of mesoderm and neural crest cells, the latter contributing to the ganglia (Bruska & Wozniak, 2000; Wikstrom & Anniko, 1987). Cells within the ganglia differentiate into both neural and supporting glial cells. The neural cells eventually develop a bipolar morphology, extending central processes toward the neural tube and peripherally into the sensory epithelium of the vestibular apparatus and cochlea. Ganglionic neuron processes extend centrally toward the neural tube region that will form the medial geniculate nuclei. Divisions of the cochlear ganglion (spiral) from the vestibular ganglion have been identified to occur in human embryos between Carnegie stages 18 and 19 (44 to 46 postovulatory days; Ulatowska-Blaszyk & Bruska, 1999). Growth of processes toward the sensory epithelia is potentially driven by chemoattractant and repulsion cues (for a review, see Fekete & Campero, 2007). The neurotrophin family and their high-affinity Trk receptors control innervation of the cochlea during embryonic development. Mouse models point to a role for both brain-derived neurotrophic factor (Bdnf) and neurotrophin 3 (Nt3; Schimmang et al., 2003).

In humans, the cochlea nerve fibers in the prosensory domain appear at Week 6 and commence synaptogenesis in Week 9 (Pechriggl et al., 2015). The ganglion neurons differentiate to form two distinct populations on the basis of their location within the ganglia and soma size, central Type I large and peripheral Type II small cells. Note that more Type II ganglion cells have been identified in neonates, within the middle and apical turns, than in adults (Chiong, Burgess, & Nadol, 1993). This suggests an ongoing postnatal differentiation within the ganglion. An earlier study identified the associated glial cells do not myelinate the ganglion fibers, either in the fetus or neonate, and only thin myelination was observed in the elderly (Arnold, 1987). A more recent study identified in the fetal period cochlear, Schwann cell myelination (24 weeks) distally, and a later glial myelination (26 weeks) proximally (Moore & Linthicum, 2001).

In the fourth week, the endolymphatic sac extends initially from the otic vesicle as a small diverticulum, with the main otic body forming the primordia of the utricle and the saccule (Figure 1–3). Regional differentiation of the utricle and saccule is regulated by the transcription factors Otx1 (Beisel, Wang-Lundberg, Maklad, & Fritzsch, 2005) and Pax5 (Kwak et al., 2006), both members of the homeobox gene family. The endolymphatic sac's mature function is both secretory and absorptive. The endolymphatic sac begins initially as an extending "single-lumen pouchlike structure," which in humans goes on to develop through the fetal period and into the first postnatal year into a series of tubular structures (Bagger-Sjoback, 1991; Ng, 2000; Ng & Linthicum, 1998). This mature tubular structure is not seen in other species (Ng & Linthicum, 1998).

The adult endolymphatic sac is filled with endolymphatic fluid with a unique composition of high potassium and low sodium ions (Grunder, Muller, & Ruppersberg, 2001). Both the vestibular and cochlear epithelial cells secrete endolymphatic fluid. It is not known in humans at what stage of development this ionic status is achieved. In the rat, adult sodium levels are seen in the first week after birth, while both potassium

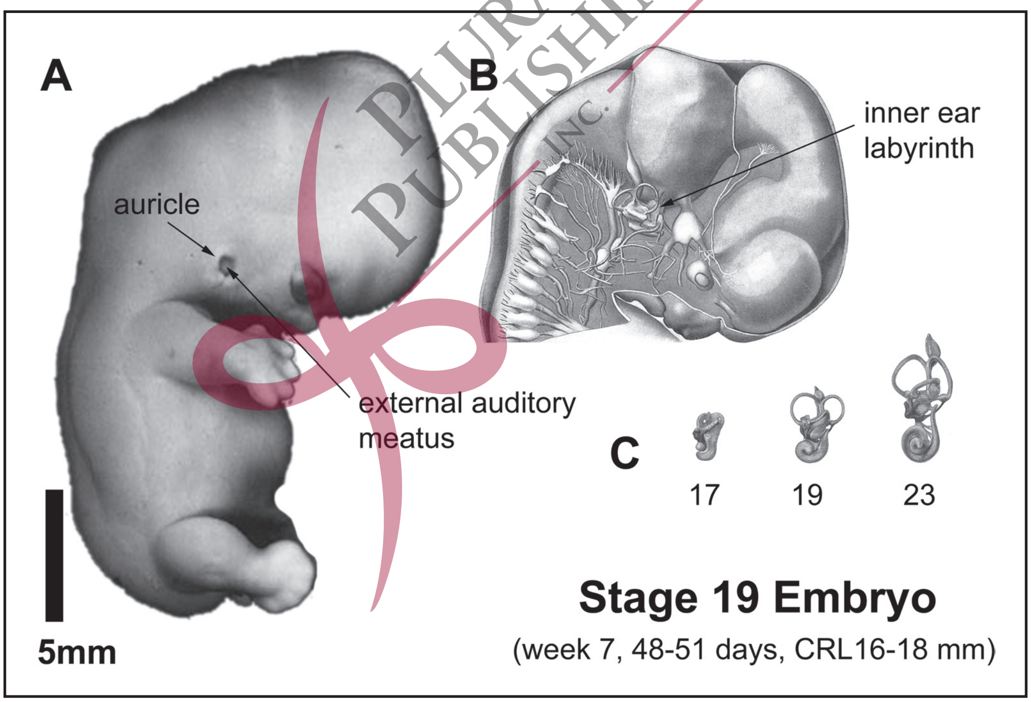

FIGURE 1–3. Stage 19 embryo (Week 7) showing the ear development features. **A.** Lateral view of the whole embryo with 5-mm scale bar. Note the pharyngeal arches have differentiated and are no longer visible on the surface. The external ear (auricle) has formed from hillocks on pharyngeal arch 1 and arch 2. Note the relative position of the ear just above the neck and at the level of the lower jaw. The external auditory meatus is enlarged and ends at a meatal plug. **B.** Historic image (Thyng, 1914) cutaway view of same stage embryo showing the position and appearance of the inner ear relative to the developing brain and other cranial ganglia. **C.** The relative size and shape of the inner ear labyrinth at Weeks 6, 7, and 8. By the end of the embryonic period (Week 8), the inner ear labyrinth approximates the shape of the adult structure.