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of
Sensory Physiology*

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Chapter 5

Ontogeny of Structure and Function in the Vertebrate Auditory System

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With 15 Figures and 4 Tables

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A. Introduction

Why study the vertebrate auditory system? Throughout the ages, when scholars have attempted to define objectively the qualities that distinguish man from other animals, the power of human communication systems inevitably comes to the fore. Normal development of auditory perception is essential for the

establishment of both expressive and receptive aspects of language. Thus, increased understanding, leading to eventual prevention or treatment of the various conditions that cause failures in the normal processing of acoustic information, has important clinical relevance. Furthermore, the auditory system is one of the primary sense modalities, involving both a highly specialized peripheral receptor organ and a complex set of central pathways.

Thus, ontogenetic studies of the vertebrate auditory system are of general importance. For instance, studies of the sensory epithelium and associated peripheral specializations are important for understanding the origins, inductive interactions, and polarization gradients of receptor specializations. Analyses of central nervous system pathways will lead to increasing understanding of the ontogeny of neural coding mechanisms and the role of afferent innervation and/or stimulation in the ontogeny of neural networks. Finally, investigations of an organism's behavior with respect to its acoustic environment will expand our general knowledge of how organisms come to appropriately organize and categorize their sensory environment.

The present review attempts two tasks related to the functions noted above. First, a large portion of the literature on the ontogeny of auditory system structure and function is brought together and summarized in Tables 1-4. The tables, forming the body of this review, are meant to provide access to the various areas of literature and to provide brief summaries of what I believe to be the major findings derived from each group of studies. The text and figures accompanying the tables are intended to point out areas of controversy and agreement, and areas where future research will be most beneficial. It should be pointed out that the tables and text do not exhaustively cover all the literature in this field. Several areas of research have been intentionally omitted or receive only abbreviated treatment because they have been adequately summarized elsewhere, or due to limitations of space and time. Where possible I have attempted to point out these omissions in the text and to cite a few general references in these areas. In addition, in some cases where the same data appear in many sources by the same author(s), only the most inclusive paper has been cited. Finally, there are undoubtedly omissions in areas that are intended to be exhaustive¹.

The second purpose of this review is to point to some examples of research areas where investigations of auditory system development either have had, or can have, relevance for broader problems of behavior or brain development. Thus, the second section gives brief summaries of three research programs in which the vertebrate auditory system is used to approach general problems of neural and perceptual ontogeny. The examples chosen are the research of G. GOTTLIEB, D. KENT MOREST, and the present author.

¹ I would appreciate being informed of any such omissions, as I will attempt to maintain and make generally available a complete list of citations relevant to the area of auditory system development.

B. Ontogeny of the Auditory System

I. Embryology of the Auditory Receptor²

1. Early Development of the Inner Ear

Table 1 summarizes the literature on the ontogeny of the vertebrate inner ear. The early literature was reviewed by MINOT (1892), while later reviews concentrated on selected topics. BAST and ANSON (1949) present a detailed account of normal morphogenesis and histogenesis in mammals, especially man. ALTMAN (1950) presents a briefer but excellent account of normal development, and includes much of the comparative and experimental literature. YNTEMA (1955) summarizes the work on amphibians, dealing primarily with inductive interactions and polarization of the ear and surrounding tissue, and VAN DE WATER and RUBEN (1976) present an up-to-date account of the experimental research in this area. Table 1 is restricted to inner ear and ganglion cell development, and does not include the following related topics: induction and differentiation of otic capsule and surrounding tissues (YNTEMA, 1955; VAN DE WATER and RUBEN, 1976); ontogeny of the middle ear (BAST and ANSON, 1949; CANDIOLLO and LEVI, 1969; STEPHENS, 1972); and pathological abnormalities, including those of known genetic origin (BAST and ANSON, 1949; HARDY, 1975; VAN DE WATER and RUBEN, 1976).

The earliest embryological sign of an auditory apparatus is a thickening of the ectoderm on either side of the head at a rostrocaudal level approximately at the middle of the hindbrain. This thickening, first recognized as the anlagen of the inner ear by HUSCHKE (1831), is the auditory placode. It will eventually become the entire otic labyrinth, a continuous series of epithelium-lined tubes housing the auditory and vestibular organs. The placodal region invaginates to form the auditory pit, which then splits off from the overlying ectoderm to form the auditory vesicle or otocyst. These processes and the ensuing evagination of the otocyst into three primary ducts (endolymphatic duct, utriculus, and sacculus) have been described for many species, and timetables are often given (see Table 1, A.). Perhaps the best description is provided by BAST and ANSON (1949). The cochlear duct forms as an outgrowth of the rostromedial portion of the sacculus. Although it has not been firmly established whether cell addition occurs preferentially at the saccular (basal) or apical end during cochlear duct outgrowth, RUBEN (1967), using the ³H-thymidine negative-labeling method in mice, found that cells that had gone through their terminal mitosis earliest (oldest cells) were located at the apical end of the mature cochlea, while younger cells were located at progressively more basal portions. These data led RUBEN to hypothesize that "the growth area might be at the junction of the cochlear duct and the primitive saccule" (p. 39). To the knowledge of the present author, these results have not been replicated in other species, nor has the hypothesis been adequately tested by

² Phylogeny of the auditory receptor is not discussed in this chapter. The reader is referred to the excellent discussion by WEVER (1976).

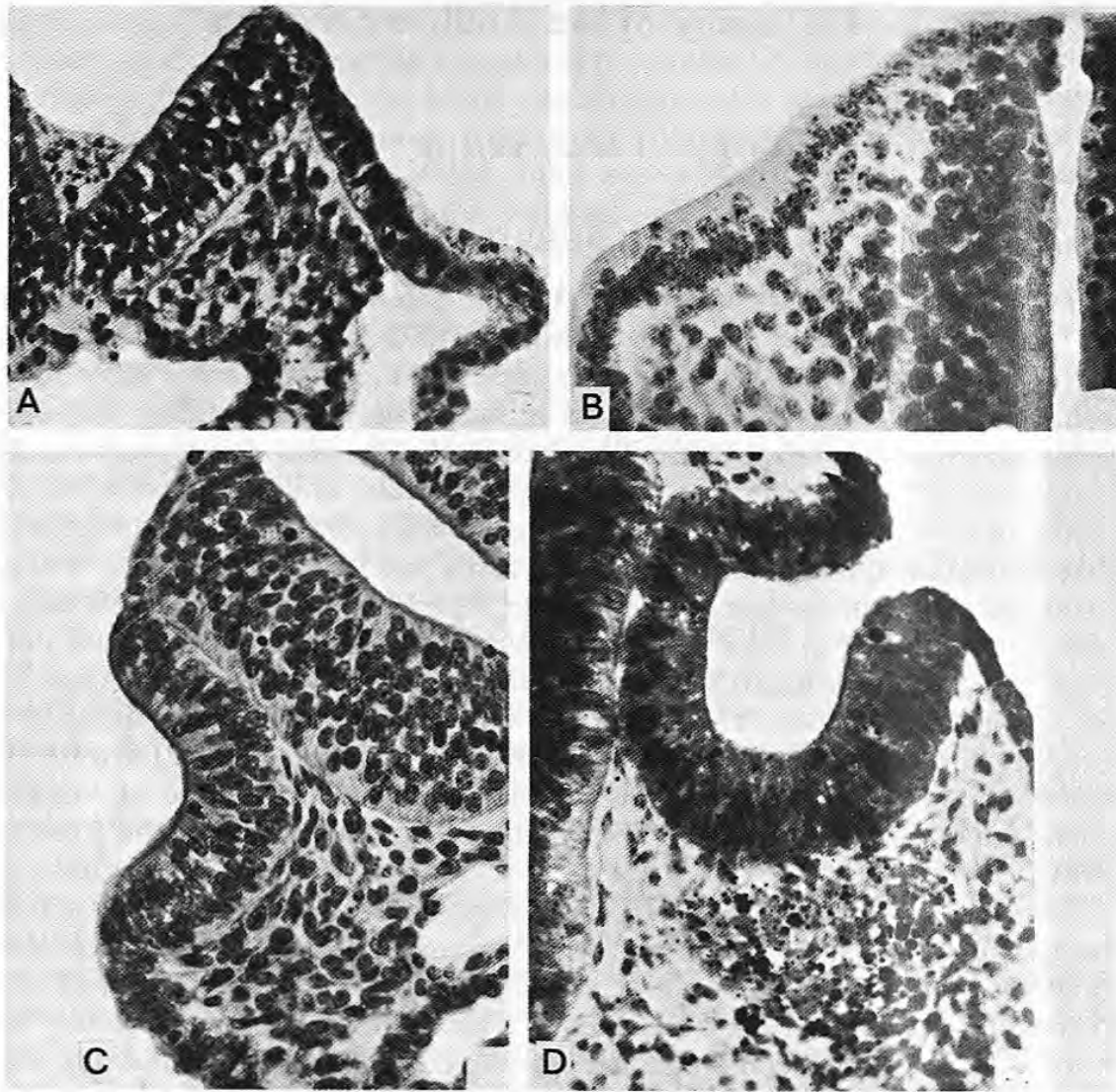


Fig. 1A-D. Taken from O'RAHILLY (1963) this figure shows the early stages of otocyst formation in the human embryo. Numbers at the lower right of each micrograph indicate embryonic stage. Magnification of all photomicrographs is about $\times 250$. (A) Two-somite (about 20th post-ovulatory day) embryo. Section through right rhombencephalon. Otic region seen as lateral (right side) continuation of rhombencephalon. Mesenchymal tissue lies between otic region and neural ectoderm; (B) 10-somite (about 22-day) embryo. Section through left neural tube. Cell bodies of otic plate occupy basal position, no thickening of plate has occurred; (C) 16-somite (about 24-day) embryo. View through left neural tube and left otic region. Extensive cell division has led to thickening and partial invagination of placodal region, forming an otic pit. Note juxtaposition of otic pit and neural tube; (D) 24-somite (about 26-day) embryo, right otocyst and edge of neural tube. Continued cell division and invagination has produced an otic vesicle. Only a narrow pore extends between the cavity and surface of the embryo. Vesicle in close contact with rhombencephalon (left). Note cells below vesicle; these are probably early neuroblasts of the VIIIth nerve ganglia

investigating proliferative zones at various stages of cochlear duct outgrowth. In addition to providing additional information concerning cell addition, such investigations might shed light on the mechanics of spiral formation, e.g. cell proliferation around the duct may occur at unequal rates.

Inductive interactions involved in the early stages of otocyst development have been extensively studied in amphibians, and to a lesser extent in chick and mouse

embryos. The first interaction noted in the literature involves the placodal region and the chordamesoderm, which during gastrulation comes to lie under the presumptive auditory field. Transplantation and *in vitro* experiments have firmly established that the underlying mesoderm plays an important role in differentiation of the placodal region and in the early stages of vesiculation.

Following invagination, the vesicle lies in very close apposition to the rapidly developing neural folds. At this stage, the rhombencephalon exerts a powerful influence on further development. In amphibians, the experimentally induced absence of a hindbrain causes the vesicle to remain cystic, and histogenesis is minimal. The inductive role of the rhombencephalon in mammalian otocyst differentiation is more difficult to determine experimentally, but is strongly supported by two lines of research. First, the remarkably close apposition between the developing otocyst and the neural folds is present in man and other mammalian species as well as amphibian and avian embryos (Fig. 1). Second, in several strains of mutant mice, where a primary etiology is thought to be a malformation of the rhombencephalon, the inner ear fails to form normally (VAN DE WATER and RUBEN, 1976). The next phase of investigation in this area will undoubtedly be to determine the biochemical nature of the above tissue interactions. Unfortunately, in the ontogeny of the otic labyrinth, the interactions of biochemical, mechanical, and hydrostatic factors will be unusually difficult to work out. On the other hand, the re-emergence of *in vitro* analyses, especially in conjunction with mutant strains and microsurgical manipulation, holds great promise for this area of research (see VAN DE WATER and RUBEN, 1974).

Investigations of polarization of the ear have been essentially nonexistent in the last 30 years. Earlier studies have shown that rotation or disharmonic transplantation of the placodal ectoderm in amphibians can lead to a variety of results, including dwarfed structures, reversal of normal polarity, or mirror-image reduplication of either the rostral or the caudal half, depending on the age at which the manipulation takes place or the ages of donor and host embryo. In light of the current interest in embryological gradients, it is somewhat surprising that no recent studies have utilized *in vitro* methods in combination with biochemical analyses and/or manipulations in attempts at further study of the nature of the polarization gradients. Furthermore, since the inner ear is composed of several different organs with distinct central connections, investigations of the nature of the central connections, influences on target cells, or behavior effects of manipulating the polarization are in order.

There is also a relative paucity of literature concerning the proliferation of cells in the organ of Corti. An elegant contribution by RUBEN (1967) is the only investigation of proliferation of the various cell types. Two aspects of this study merit additional discussion and future attention. First, it was found that the majority of cell types in the organ of Corti of mice all underwent their terminal mitoses on the 14th day of gestation. These included spiral ganglion cells, inner hair cells, outer hair cells, inner pillar cells, outer pillar cells, Deiter's cells, Hensen's cells, Claudius' cells, inner supporting cells, and external sulcus cells. This remarkable synchrony of structurally and functionally divergent cell types suggests to this author either a common origin or some active process regulating the synchronization of proliferation. Also of considerable interest is the finding (noted

above) that the organ of Corti demonstrates an apical-to-basal proliferation gradient; that is, the first cells to go through their terminal mitosis are found near the apex, while later-dividing cells are distributed at progressively basal locations. This finding is somewhat surprising when considered in conjunction with the facts that the spiral ganglion cells show an opposite (basal-to-apical) proliferation gradient, and virtually all other aspects of cochlear and central nervous system differentiation show a basal-to-apical sequence (see below). In later investigations, RUBEN and his colleagues have utilized short-term exposure to ^3H -thymidine to investigate cellular kinetics in the inner ear of normal and mutant mice. These investigations led to the demonstration that the pattern of nuclear migration is similar to that found in the neural tube; synthetic activity occurs near the basement membrane and mitosis at or near the lumen. In addition, observations on the Kreisler mouse (Kr/Kr), which is known to suffer aberrant rhombencephalon development, suggest a neural influence on cellular proliferation in the inner ear. These pioneering studies by RUBEN have, therefore, raised many important questions regarding the cellular dynamics responsible for normal and abnormal cochlear development. Additional studies, focusing on the neural regulation of cell proliferation, the origins of the various cochlear cell types, and cellular migration within the cochlear duct will yield valuable information for understanding developmental anomalies of the inner ear.

2. Differentiation³ of the Organ of Corti

Although adequate means for identifying proliferation times of unidentified cell types became available only recently, examination of tissues during development has been a chief pastime of both embryologists and comparative anatomists for centuries. Thus it is not surprising that within 10 years of the time when Corti provided the first detailed description of the organ that bears his name, KÖLLIKER (1861) published the first description of its development in man. Since that time well over 100 papers have described the differentiation of the organ of Corti in most vertebrates. What may be surprising, in view of the technical advances in fixation, microscopy, and staining over the last 100 years, is that the most detailed descriptions of the final stages of this differentiation are still those in RETZIUS's two-volume opus, *Das Gehörorgan der Wirbelthiere* (1884). In Fig. 2 one of his magnificent plates has been reprinted, showing the basal, middle, and apical turns at three stages of development in the cat. Figure 3 is included for identification of the major cell types.

Inspection of Table 1, Section D, quickly reveals the principal findings on histological differentiation of the organ of Corti. The majority of studies present an ontogenetic timetable of the normal appearance of the organ for the species in question. The fundamental principles shown by these studies are: i) Histological differentiation of all elements at a given cochlear location occurs in synchrony; ii) Differentiation occurs first in the basal turn and proceeds apically; and iii) Differentiation of inner hair cells slightly precedes that of outer hair cells.

³ "Differentiation" in this chapter refers to an ongoing histological or morphological process, not a particular state or stage of development.

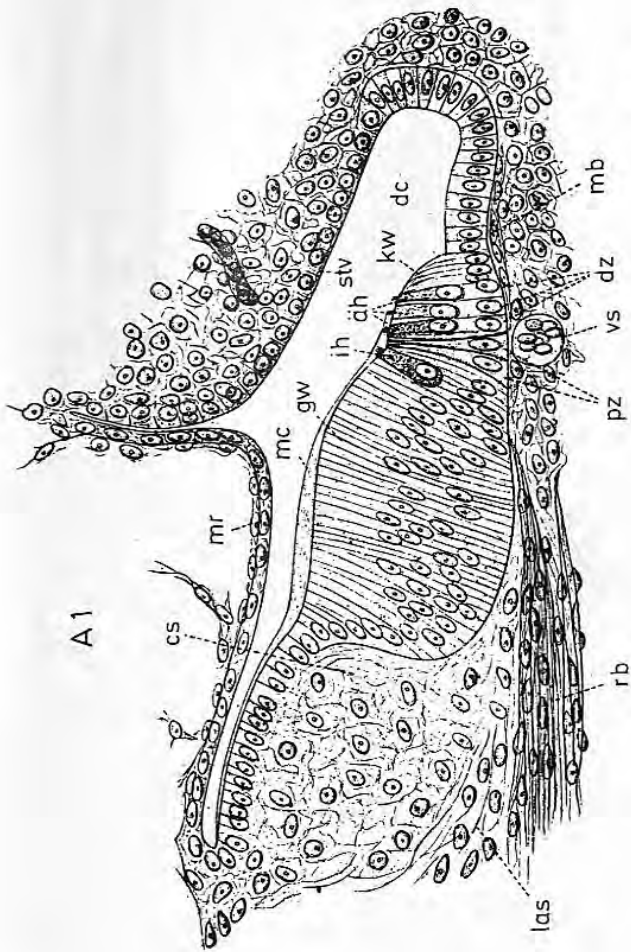


Fig. 2 A1

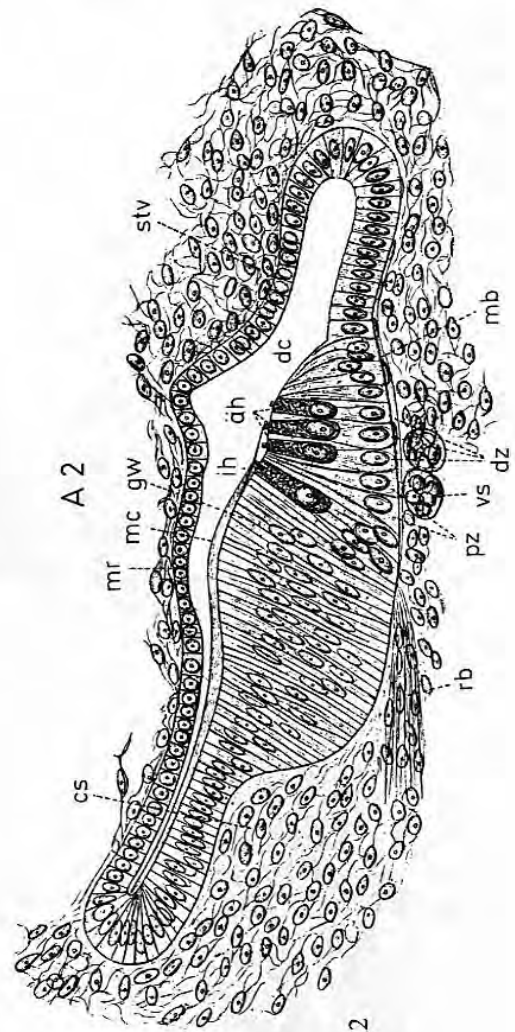


Fig. 2 A2

(Legends see p. 148)

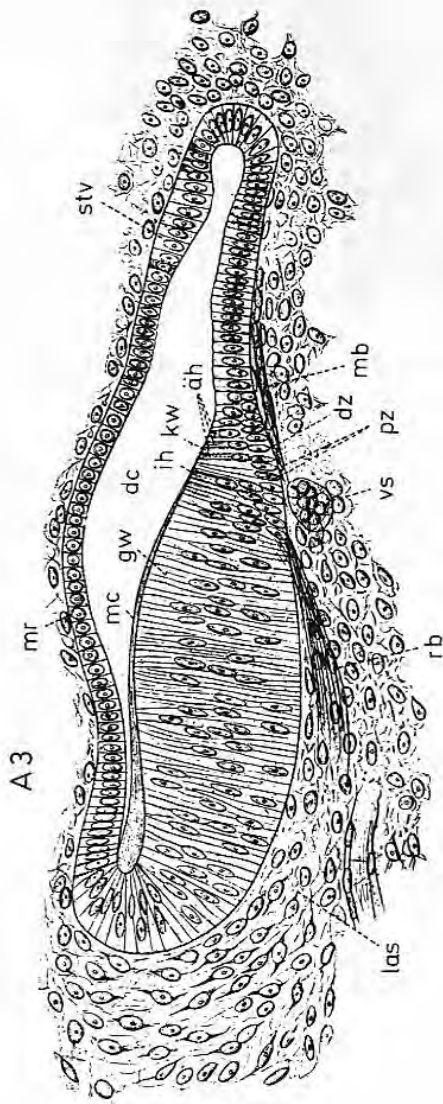
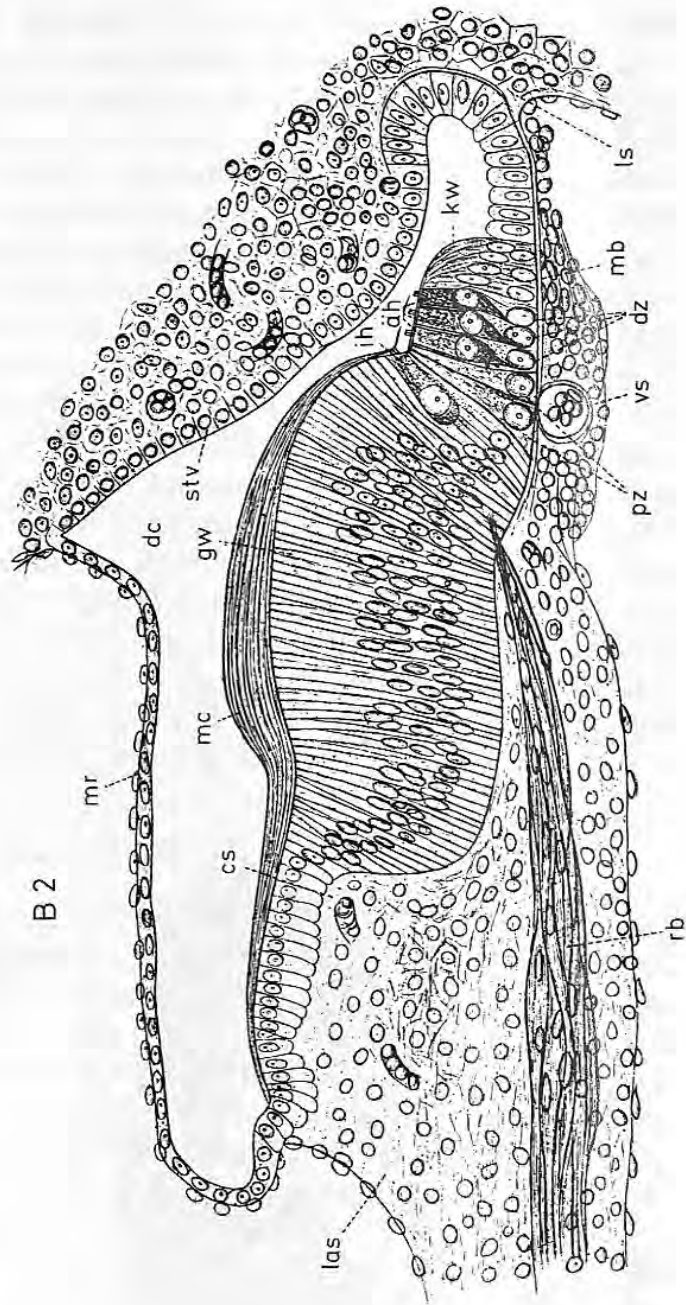


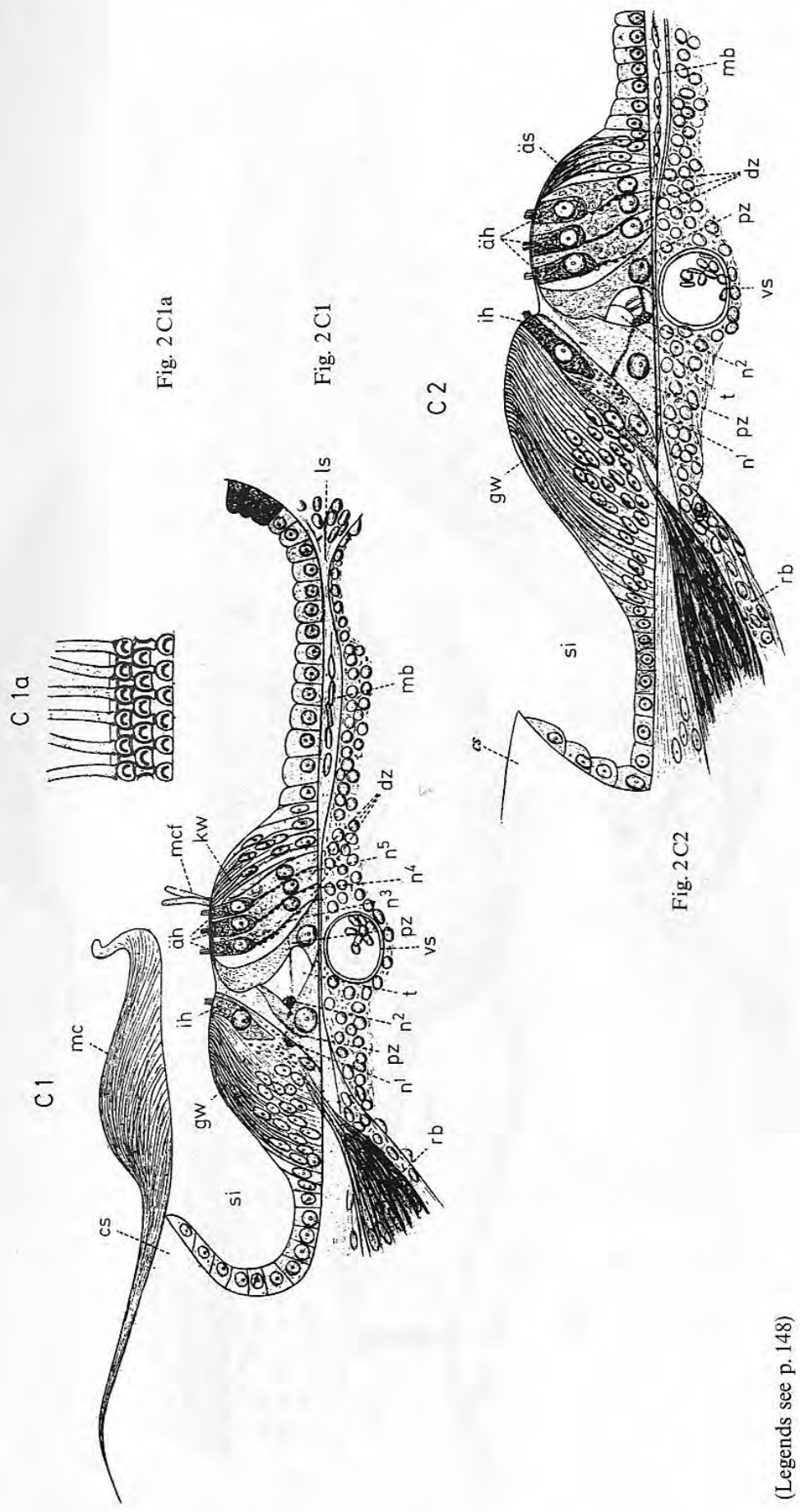
Fig. 2 A3



B 2

Fig. 2 B2

(Legends see p. 148)



(Legends see p. 148)

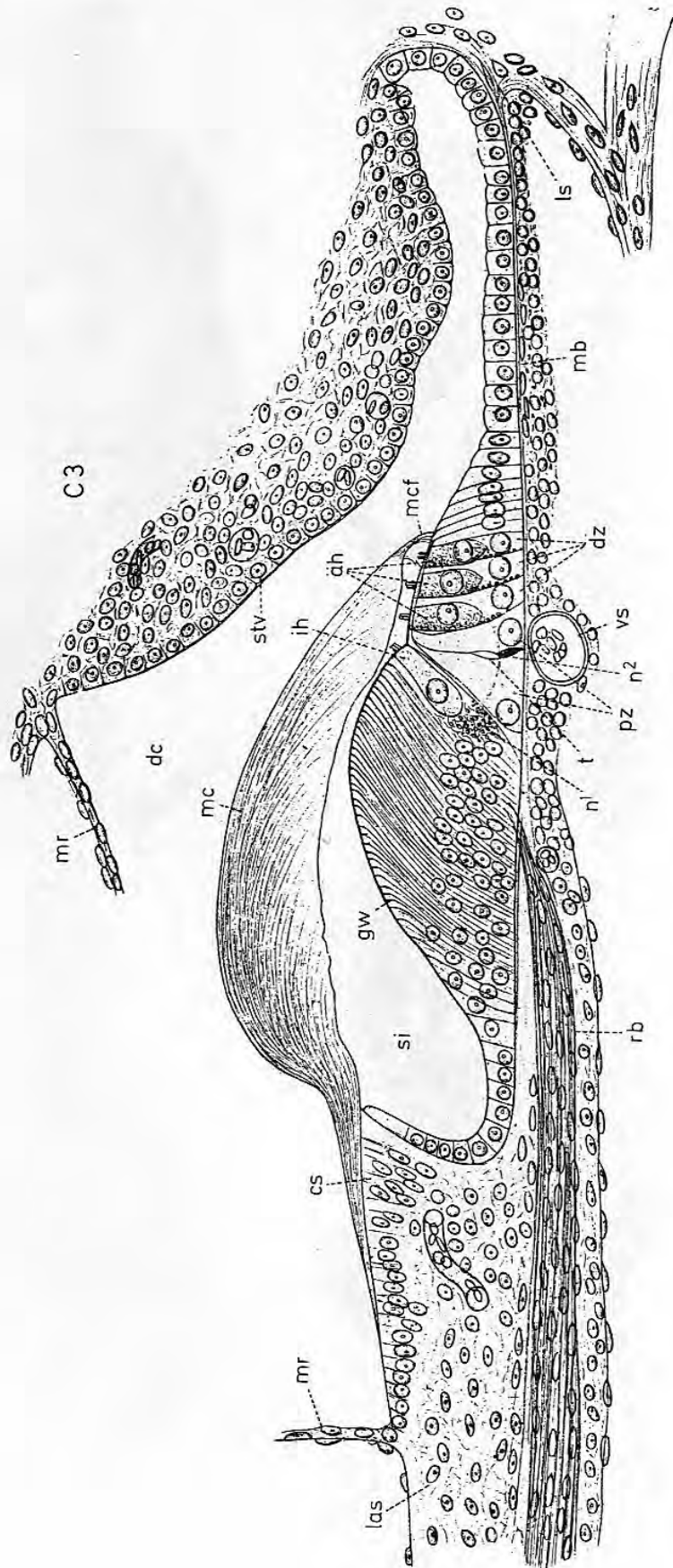


Fig. 2 C3
(Legends see p. 148)

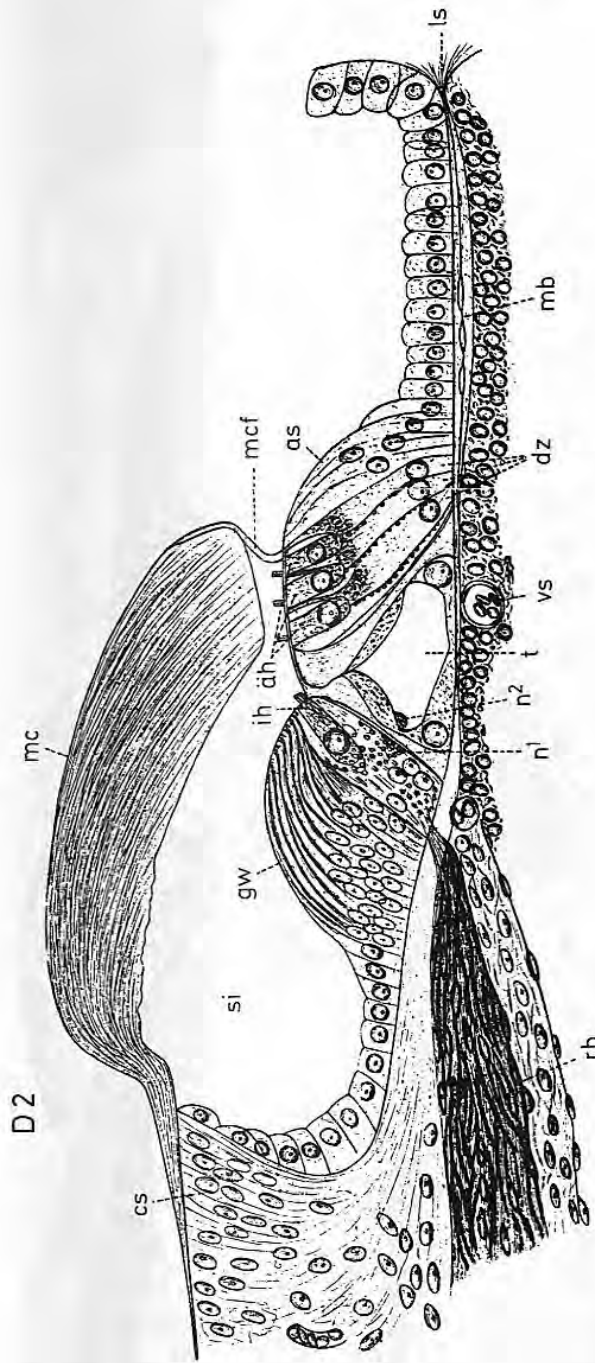


Fig. 2 D2

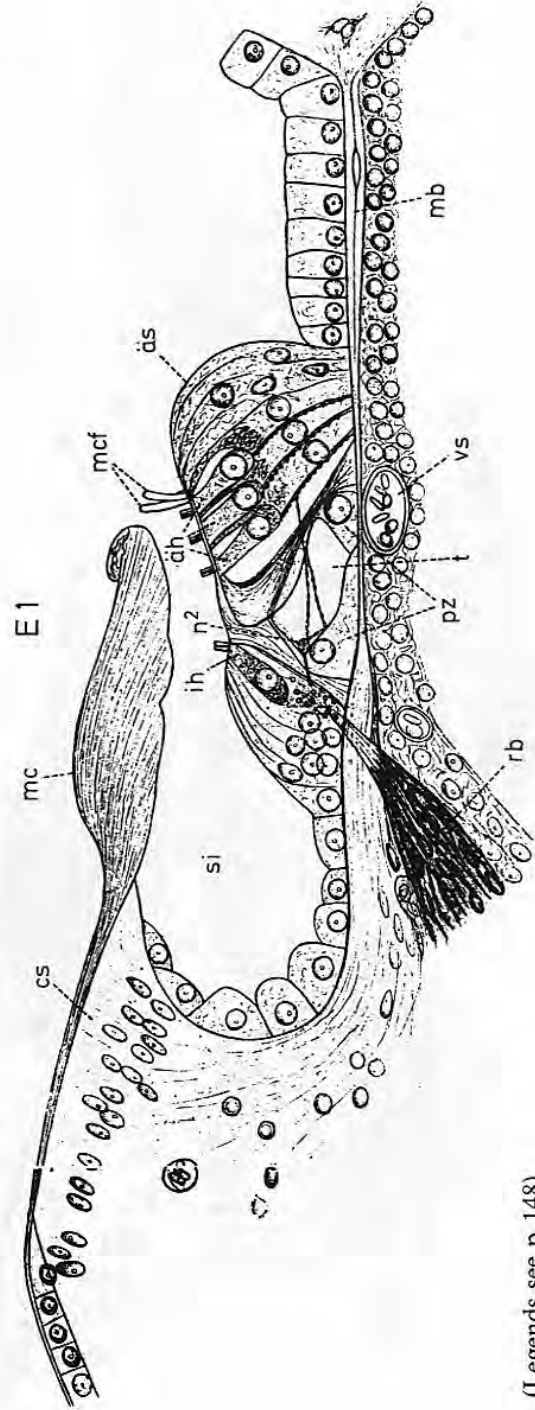


Fig. 2 E1

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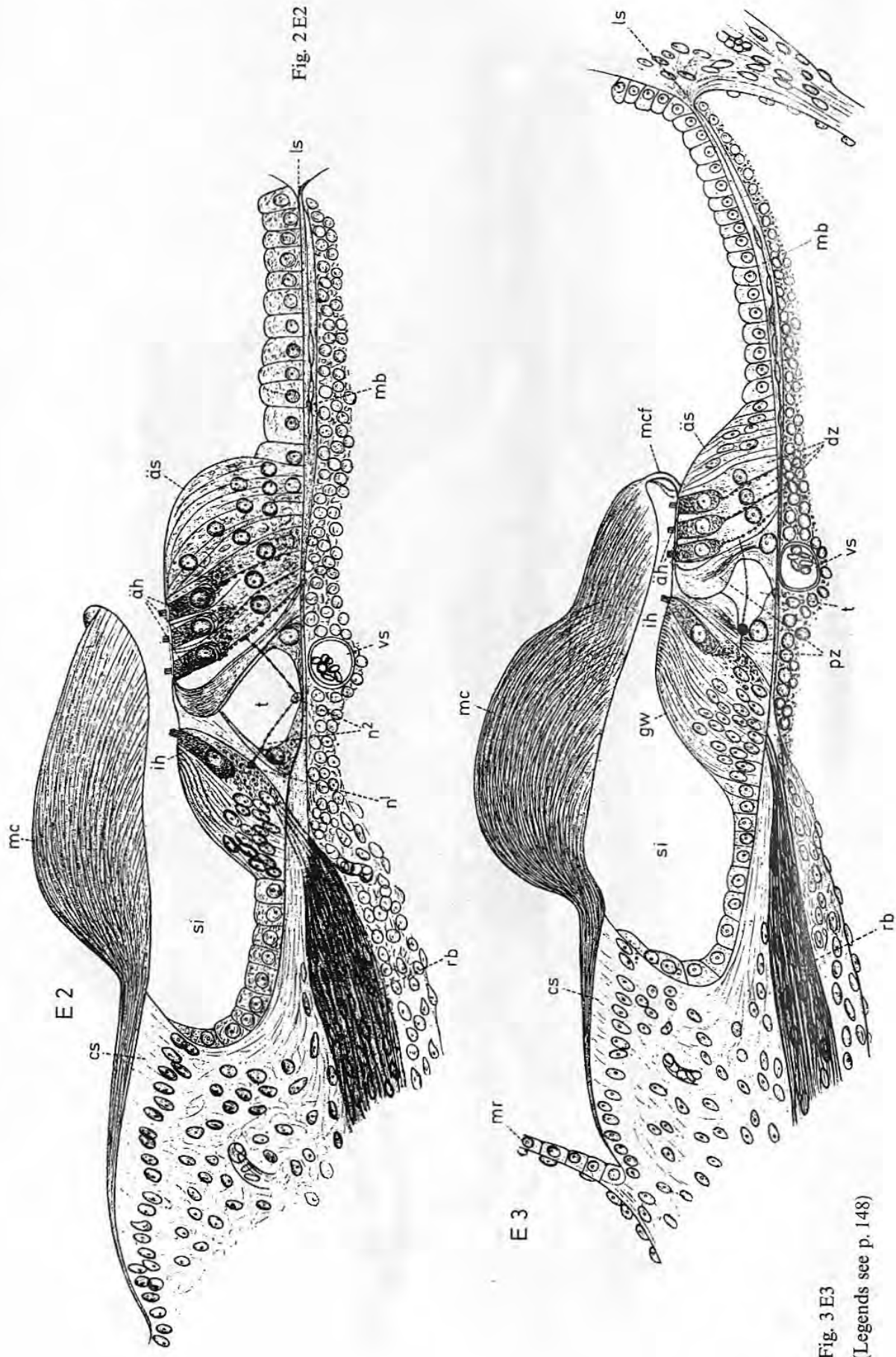


Fig. 3 E3
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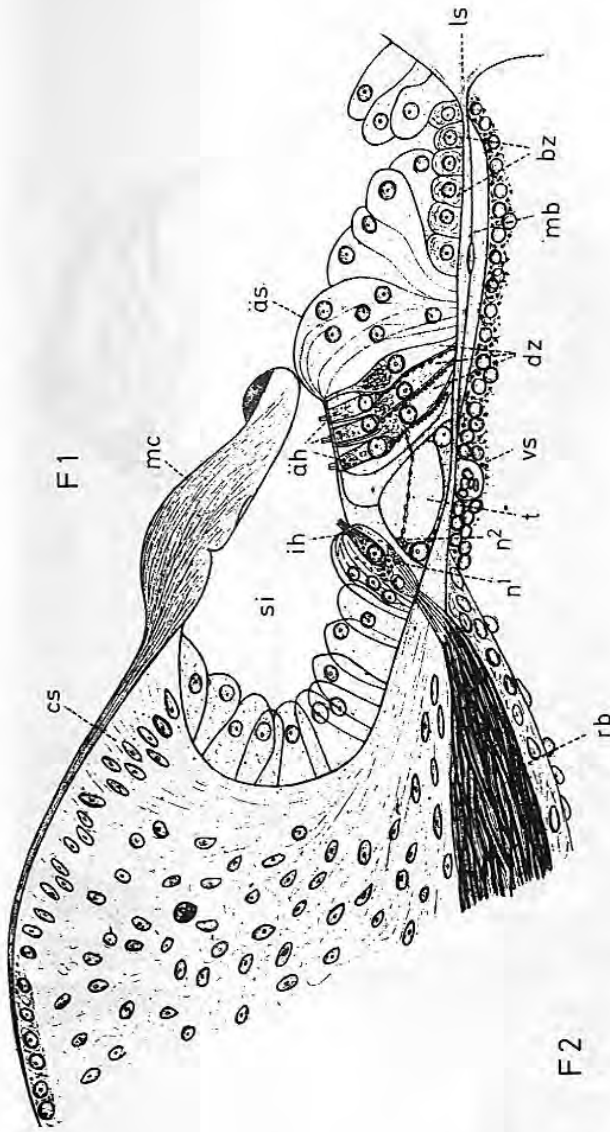


Fig. 2 F1

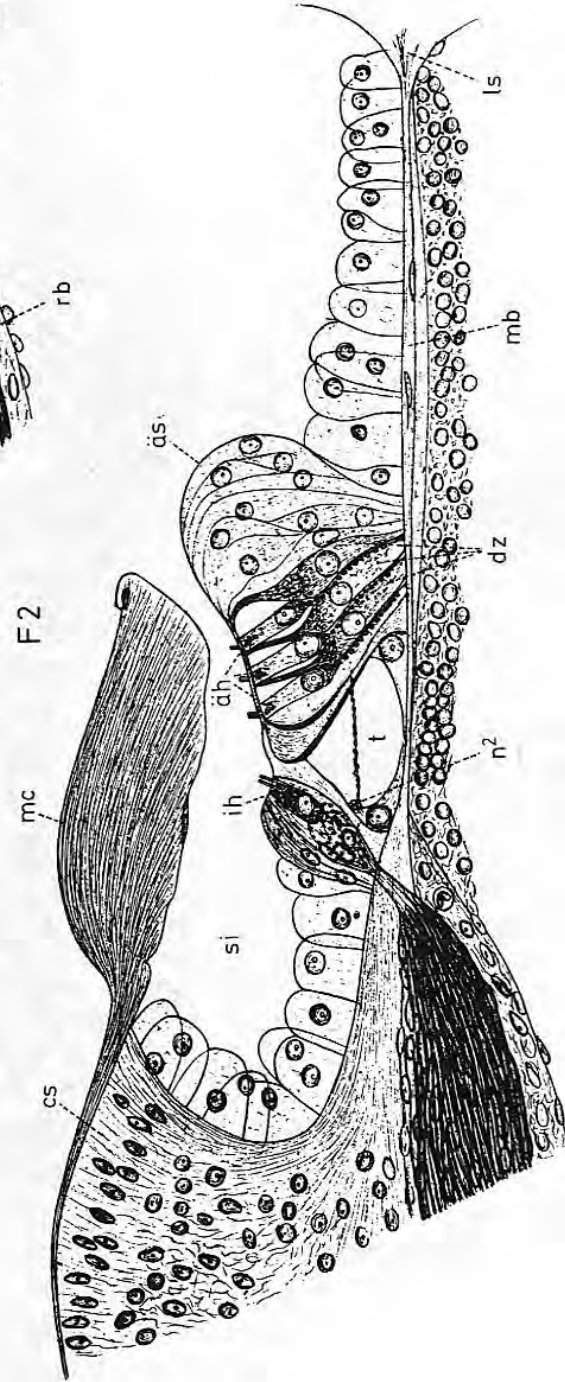


Fig. 2 F2

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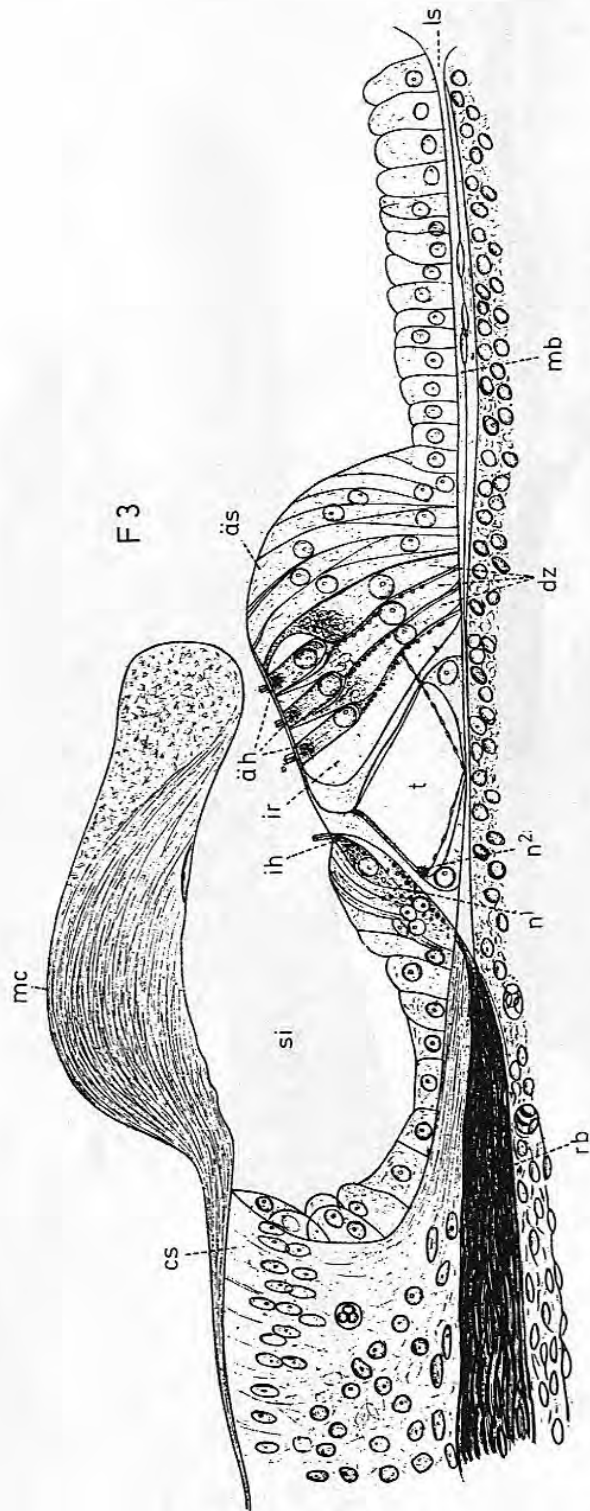


Fig. 2 F3

Fig. 2. Reproduction of lithographs (Nos. 30 and 31) from RETZIUS (1884), showing differentiation of kitten organ of Corti. Figure labeled "A" from 8-cm embryo; "B" from 12-cm embryo; "C" from newborn kitten; "D", "E", and "F" from 7-day-, 11-day-, and 30-day-old kittens, respectively. Numbers (1, 2, or 3) next to each letter (e.g. Fig. A1) refer to basal turn, middle turn, and apical turn respectively. For identification of individual structures see Fig. 3

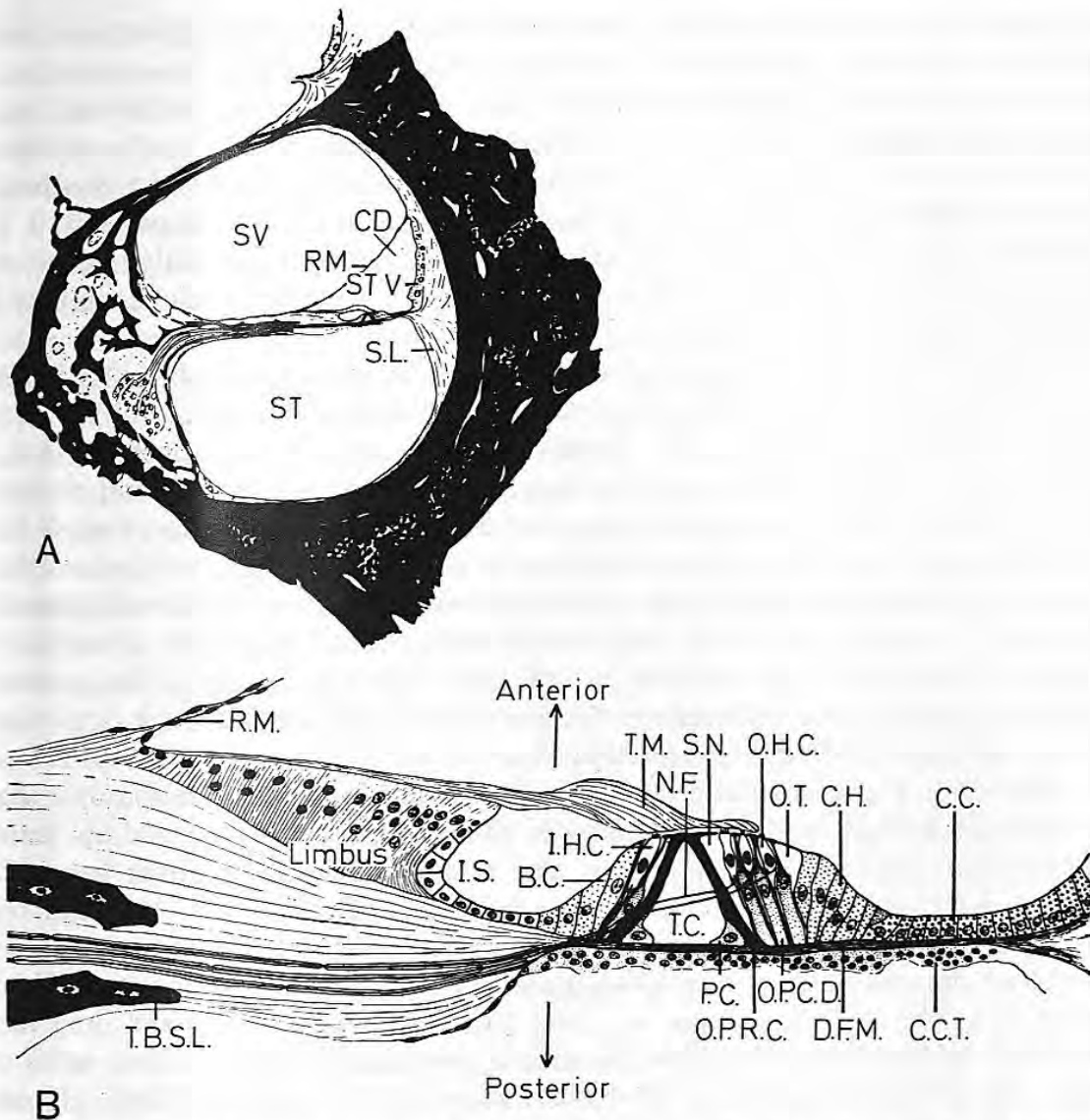


Fig. 3A and B. From BAST and ANSON (1949), Fig. 46. Drawings of horizontal section through middle turn of cochlea from 6-month-old human infant. (A) General structure of cochlea (magnification about $\times 16$). Abbreviations: CD, cochlear duct; RM, Reissner's membrane; SL, spiral ligament; ST, scala tympani; STV, stria vascularis; SV, scala vestibuli; (B) Detailed structure of organ of Corti, semidiagrammatic (approximately $\times 220$). Abbreviations: B.C., border cell; C.C., cells of Claudius; C.C.T., cellular connective tissue; C.H., cells of Hensen; D.F.M., dense fibrous membrane; I.H.C., inner hair cell; I.S., inner sulcus; N.F., nerve fiber; O.H.C., outer hair cell; O.P.C.D., outer phalangeal cell of Deiters; O.P.R.C., outer pillar rod of Corti; O.T., outer tunnel; P.C., pillar cell; R.M., Reissner's membrane; S.N., space of Nuel; T.B.S.L., tip of bony spiral lamina; T.C., tunnel of Corti; T.M., tectorial membrane

The synchronous development of cellular and morphological aspects of the organ of Corti is evident throughout this literature, but perhaps the best example is to be found in WADA (1923). In this extensive quantitative study on the ontogeny of the organ of Corti in the rat, WADA demonstrated remarkable developmental synchrony of hair cells, supporting cells, and numerous morphogenetic measures. Since WADA's work, histochemical measures on the organ of Corti and *stria vascularis* of the rat have provided additional data supporting this observation.

The finding of synchronous differentiation of functionally related cell types is not new in itself, but does suggest that either intercellular regulation of development or some additional controlling factor may be present. Furthermore, it is interesting to note that the maximal period of histological differentiation also coincides with the onset of auditory function. The possible causal relations between the structural and functional differentiation will be more fully discussed below, but it is important to point out that developmental synchronies of functionally related cell groups are common (cf. BURR, 1932; RUBEL et al., 1976). Often a relationship with functional ontogeny is suggested.

Without doubt, the most frequent conclusion of studies on differentiation of the organ of Corti is that differentiation begins in the basal portion and proceeds apically. This relationship can be clearly seen in Figure 2, and appears true for each aspect of cellular differentiation that has been investigated. Several authors (cf. BREDBERG, 1968) have noted upon close examination that this gradient is not unidirectional; the differentiation begins near the middle of the basal turn rather than at the basal pole. In any case, the unanimous observation of a developmental gradient, in conjunction with the finding that the endocochlear potential is uniform throughout the cochlea at all ages, strongly suggests that neither hormonal changes nor a change in the general ionic environment are regulating the developmental synchrony noted above.

The slight developmental precedence of inner hair cell differentiation over that of outer hair cells has been confirmed by many investigators, and in many mammalian species. This sequence is also true of innervation; inner hair cells receive innervation slightly before outer hair cells (Table 1, E.). Although the significance, if any, of this finding is unclear, several additional differences between these two populations can be related, namely: only about 10% of the nerve fibers innervating the cochlea synapse on outer hair cells, whereas 90–100% innervate the inner hair cells [note that the mammalian cochlea has three or four times as many outer hair cells as inner hair cells (BREDBERG, 1968)]; outer hair cells are more susceptible to chemical or acoustical trauma than inner hair cells; and inner hair cells are sustained longer in cochleopathic mutants and during old age than outer hair cells. It is interesting that the later-developing outer hair cells appear considerably more susceptible to insult and receive a small percentage of the total cochlear innervation. When the functional differences between inner and outer hair cells become firmly established, it may be possible to sort out these relationships.

The application of technical developments in histochemistry and electron microscopy to the problems of cochlear differentiation have primarily served to reaffirm the conclusions stated above. Oxidative metabolism, as expected, follows the sequence, and is temporally coincident with differentiation. Until more is known regarding the synaptic chemistry of the adult cochlea, little further progress regarding its developmental regulation is possible. Electron microscopic investigations, primarily by HILDING (1969) and his colleagues, have yielded information on the time at which efferent and afferent terminals are first observed. In addition, KIKUCHI and HILDING (1965, 1966) provided the important observation that hair cells, supporting cells, and possibly cells of the *stria vascularis*

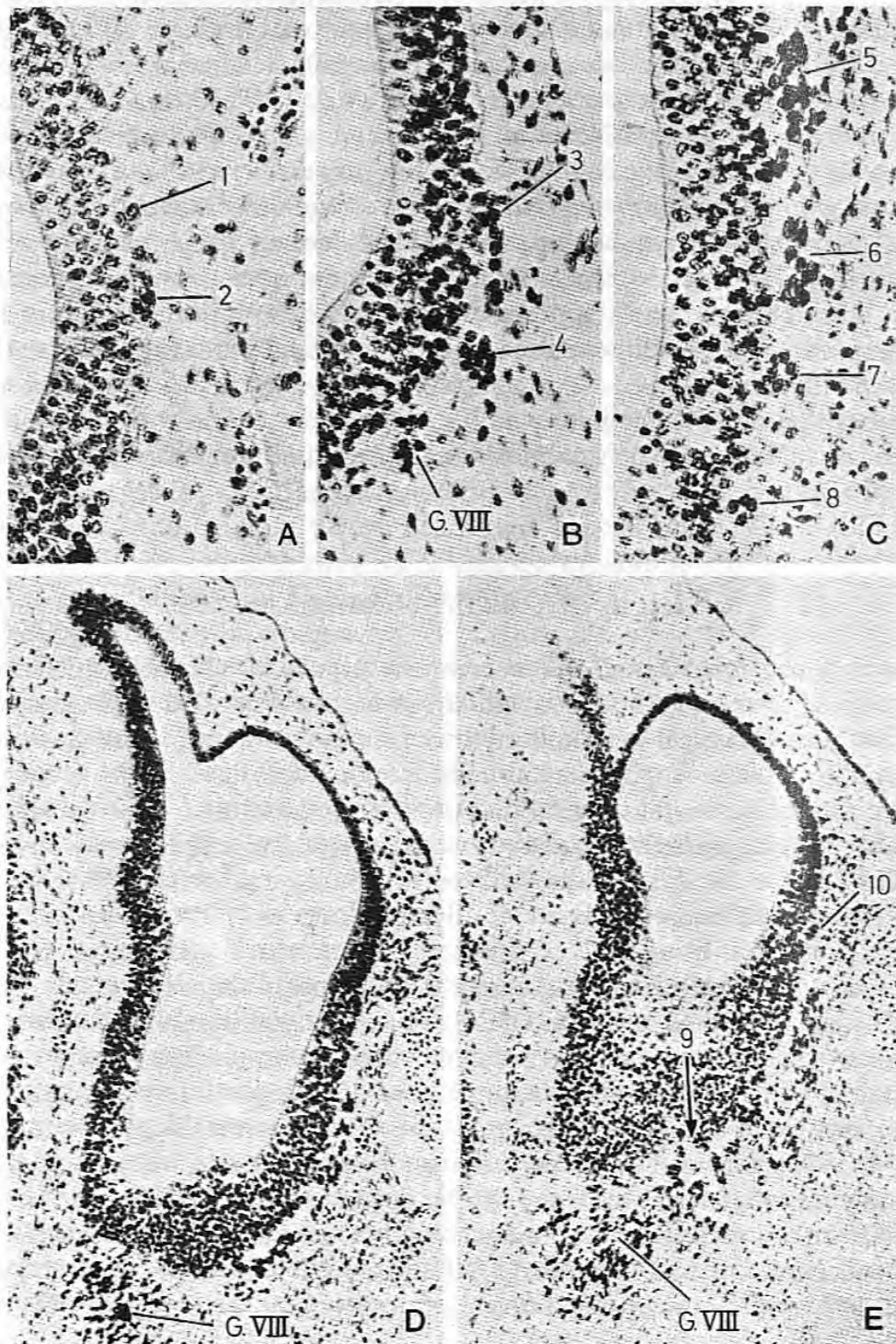
contain a single kinocilium and numerous cilia in the newborn mouse. Around the time of onset of cochlear function, supporting cells lose these structural elements and hair cells lose the kinocilium, but retain the basal body. This observation with regard to hair cells reaffirms their essential structural, and probably functional, similarities to other mechanoreceptors.

The most promising development for advancement in our understanding of the mechanisms involved in cochlear differentiation is the resurgence of research on cochlear development *in vitro*. Since the classic studies of FELL (1928–29) it has been well known that the otocyst will show relatively complete morphological and histological differentiation *in vitro*. Several laboratories are now utilizing *in vitro* preparations of the chick or mouse cochlea to investigate normal and pathological cochlear development (FRIEDMANN and BIRD, 1961, 1967; ORR, 1968, 1975; VAN DE WATER and RUBEN, 1974; SOBKOWICZ et al., 1975; ROSE et al., 1977). In addition to demonstrating that most of the ontogenetic relationships described above occur in culture, these investigators have begun to unravel the influence of intercellular environmental factors on cochlear differentiation. Most important for the present purpose is the repeated demonstration, in both mutant mouse and normal chick cultures, that the presence of nerve fibers from the ganglion cells is necessary for complete differentiation of the hair cells. In areas where nerve fibers are absent, differentiation of the organ of Corti is arrested at an immature stage. In the future it should be possible to utilize *in vitro* preparations to determine the mechanisms underlying such cellular interactions and temporal gradients in the organ of Corti.

3. Origin of Cochlear Ganglion Cells

The origin of cochlear ganglion cells has been the subject of much debate during the 20th century. From examination of histological sections and organ dissection, most classical anatomists were of the opinion that the acousticovestibular and geniculate ganglia were initially fused, and of neural crest origin. After migration from the neural tube, further proliferation and then eventual subdividing of the separate ganglionic masses were thought to occur (ADELMAN, 1925). STREETER (1906a, 1912) is usually credited with initiating the view that the VIIth and VIIIth nerve ganglion cells are not derived from a common primordium, the geniculate ganglion being derived principally from neural crest and the acousticovestibular ganglion cells arising from the ectoderm of the otic placode. Largely through the influence of ADELMAN (1925), the former view found its way into most textbooks, while during the same period noted embryologists were proving it fallacious in amphibians. Thus a large number of transplantation and extirpation studies (see Table 1, E), culminating in the Nile blue marking experiments of YNTEMA (1937), conclusively showed that in amphibians, the acousticovestibular ganglion cells are derived from the medial wall of the otic vesicle. As these cells split off from the vesicular pouch, they come in close apposition to the crest cells, which will later form the geniculate (VIIth) ganglionic mass; hence the earlier confusion. Therefore the problem appeared resolved, at least for amphibians, and

subsequent detailed examination of normal tissue in developing chick (PROCTOR and LAWRENCE, 1959), cat (HALLEY, 1955), sheep (BATTEN, 1958), and human embryos (POLITZER, 1956) all confirm that cochlear and vestibular ganglion cells are of placodal origin. As each of these authors shows an elegant series of micrographs of presumptive ganglion cells budding off from the developing otocyst (Figs. 4 and 5), general resolution of the problem was apparent.



Recently, the accepted view of placodal origin has been challenged on two grounds. On the basis of electron-micrographic evidence that nerve fibers first invade the region of the hair cells at 6—8 days in the chick embryo (*in vivo* and *in vitro*), FRIEDMANN (1969) claims that the ganglion cells are not of placodal origin; otherwise fibers would be apparent at the earlier stage suggested by PROCTOR and his colleagues. In addition to the obvious weakness of this negative argument, FRIEDMANN presents no evidence that his cultures were devoid of ganglion cells, and he clearly states that the afferent fibers are critical for hair cell differentiation. The second, and equally suspect, challenge to the view of placodal origin arises from an extensive series of investigations of cochlear differentiation in mutant mice by DEOL (1967, 1970). Examination of the inner ears of mutants known to suffer from abnormal neural crest development revealed gross malformations of the organ of Corti. From these results, DEOL reasoned that the cochlear ganglion cells were at least partially of neural crest origin, in spite of the fact that the ganglion cell degeneration was less severe and appeared secondary to that of the sensory epithelium. The primary etiology of the mutations is not known, and it is well known that the differentiation of neural crest derivatives is highly dependent on their migratory and postmigratory environment (WESTON, 1971). Thus it is highly possible that the neural crest abnormalities in these animals are secondary in nature. Furthermore, the fact that the ganglion cells themselves were largely spared in many of these animals casts serious doubt on DEOL's conclusion. At present, therefore, the present author feels that there is little or no evidence supporting a neural crest contribution to the neurons of the cochlear ganglion of any vertebrate. However, in view of the evidence suggesting two types of ganglion cells (SPOENDLIN, 1966, 1970, 1974) and the previous suggestion of dual placodal and crest origin of the trigeminal ganglion (HAMBURGER, 1961), this possibility must not be excluded until the critical experiments have been done. Such experiments, which would involve transplantation of otocysts from ^3H -thymidine labeled donors to unlabeled host embryos prior to the stage of neural crest migration, are now quite feasible in avian embryos and would presumably lay this issue to rest.

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- ◁ Fig. 4A—E. VIIIth nerve ganglion cells budding off right otocyst of sheep embryos. From BATTEN (1958). (A) Transverse section of 7.2-mm sheep embryo showing two early placodal buds (1 and 2) on medial wall of otic vesicle. Both buds appear to be sliding ventrally between parent epithelium and basement membrane. \times approx. 270; (B) Three placodal spurs associated with rostromedial wall of otic vesicle in 8.0-mm sheep embryo. Spur 3 still enclosed by tubular evagination of basement membrane, but spur 4 completely detached from epithelium. Immediately below lies diffuse tip of mass of detached placodal cells that constitute rudiment of acoustic ganglion (G. VIII). \times approx. 270; (C) Transverse section of 8.2-mm sheep embryo showing lateral wall of otic vesicle with four groups of placodal cells apparently migrating towards acoustic ganglion. Upper two spurs (5 and 6) already free of otic epithelium. Of lower spurs, 7 consists of cluster of cells probably about to detach, and 8 is small free spur attached to otic epithelium in previous section. \times approx. 270; (D) Coronal section through cranial third of otic vesicle in 8.2-mm sheep embryo. Note groups of small deeply staining placodal cells apparently migrating over lateral face of vesicle towards rudiment of acoustic ganglion (G. VIII). \times approx. 120; (E) Coronal section through same 8.2-mm embryo as Fig. 4D but passing through cranial edge of otic vesicle. Lateral groups of placodal cells have almost reached acoustic ganglion and make contact with it in next section. Arrow (9) indicates two spurs of placodal cells presumed to be streaming into ganglion. Small bud of placodal cells probably about to detach from lateral wall of vesicle is visible at 10. \times approx. 120

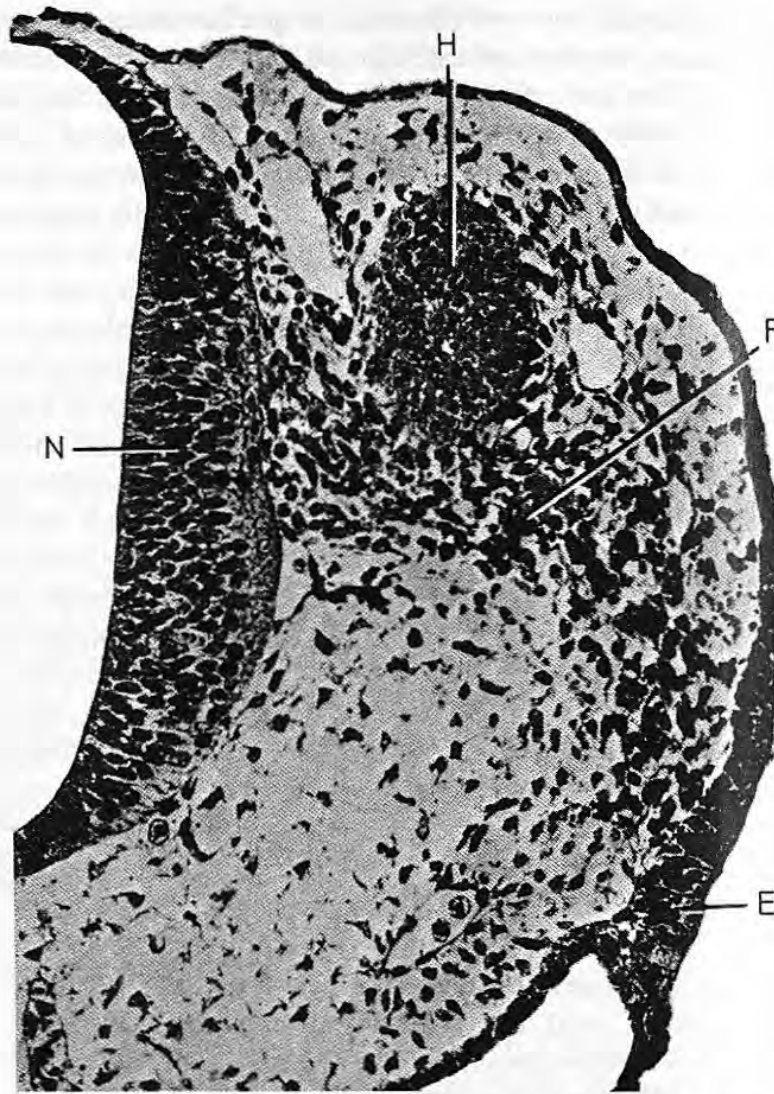


Fig. 5. Transverse section through rostral pole of otocyst (H) from 4-mm human embryo. Shows juxtaposition of otocyst to anlagen of facial ganglion (F) and to neural tube (N). Cells ventromedial to otocyst may be early cells of acoustic ganglion. From POLITZER (1956)

4. Innervation of the Organ of Corti

With osmium-fixed and reduced silver preparations, it has been repeatedly demonstrated that nerve fibers (presumably distal processes of the ganglion cells) are present in the developing cochlea at remarkably early stages. In the human, for example, fibers entering the vesicle have been reported as early as 4¹/₂ weeks of gestation. In cat, nerve fibers are apparent in the developing organ of Corti at 30 days' gestation (approximately midterm).

In both mice and chickens, where the relevant data are available, the presence of nerve fibers has been reported at times prior to the period of terminal mitosis of ganglion cells. Thus it is entirely plausible that the ganglion cells spin out their peripheral process as they migrate from the lumen of the otic vesicle, such as has been demonstrated for the axons of cerebellar granular cells. In contrast to the

Table 1. Development of the auditory portion of the inner ear

Subject of study	Species (age)	Method(s)	Comments	Relevant references
A. Formation of vesicle and growth of inner ear				
Normal growth	Human (6-16 weeks) ^a (3-20 weeks)	Light microscopy ^b Light microscopy	Cavitation of otic cavity involves chondrolysis by "histocyle" cells Timetable of otocyst formation and duct division and expansion	ANDERSON et al. (1969) BOETTCHER (1869), BAGINSKY (1886), STREETER (1906a), WILSON (1914), STREETER (1918), BARTELMIZ (1922), ANSON (1934), BAST and ANSON (1949), COOPER (1948), OMEROD (1960), O'RAHILLY (1963) HOYTE (1961)
	Rabbit (postnatal)	Light microscopy	Canals fully grown at birth	CHONDYNIKI (1968)
	Guinea pig (embryogenesis)	Light microscopy and histochemical	Timetable of normal morphological and histochemical development	TITOVA (1970)
	Sheep and goat (to 50-day embryos)	Light microscopy	Timetable of normal morphogenesis	SHER (1971)
	Mice, CBA-J/CBA-J (11-day embryo-adult)	Light microscopy	Cochlear duct first seen on 12th day; 1 $\frac{1}{4}$ turns seen by 17-18 days	STEPHENS (1972)
	Hamster (embryonic day 1-postnatal day 20)	Light microscopy	Timetable of normal inner and middle inner ear development	KNOWLTON (1967)
	Chick (embryogenesis)	Light microscopy	Timetable of normal development	WITSCHI (1949)
	Frog (metamorphosis)	Light microscopy	Changes during metamorphosis described briefly	SZEPENWOL (1933), HARRISON (1933, 1938, 1945), ALBAUM and NESTLER (1937), PASTEELS (1939), ZWILLING (1941), KAWAKAMI (1943a, b, 1949), KOHAN (1944), LEVI-MONTALCINI (1946), MOORE (1946)
Ear induction: Mesodermal	<i>Amblystoma</i> , <i>Rana</i> , <i>Triturus</i> , chick, <i>Discoglossus</i> , <i>Triton</i>	Heterotopic transplants and excision, hybrids	Mesodermal involvement in early phases of vesicle formation	

Table 1 (continued)

Subject of study	Species (age)	Method(s)	Comments	Relevant references
Ear induction: Neural	<i>Amblystoma</i> , <i>Triton</i> , <i>Rana</i> , <i>Bombinator</i> , <i>Bufo</i> , <i>Alcipenser</i> , chicken, rabbit, mouse	Heterotopic transplants, heterostatic transplants, excision, mutants, <i>in vitro</i> , X-rays	Neural involvement in ear formation, usually following vesicle invagination	STONE (1931), GUARESCHI (1935), HOLTFRETER (1935), BONNEVIE (1936), ALBAUM and NESTLER (1937), WADDINGTON (1937), SCHMIDT (1938), WATERMAN (1938), WOERDEMANN (1938), KOHAN (1939), YNTEMA (1939, 1950), TRAMPUSCH (1941), HERTWIG (1942), GINSBURG and DETLAFF (1944), BARBARETTI (1948), DETWILER (1948, 1949), DETWILER and VAN DYKE (1950, 1951), GARCIA (1961), DEOL (1966), VAN DER BORDEN (1967), FRIEDMANN (1969), RUBEN (1973), VAN DE WATER and RUBEN (1974)
Regulation of size	Chick, <i>Amblystoma</i> , <i>Rana</i>	Extirpation and heteroplastic transplants	Induction of heterotopic ectoderm or heteroplastic environmental factors can regulate ear size	WADDINGTON (1937), RICHARDSON (1932), ZWILLING (1941), YNTEMA (1955)
B. Polarization of the ear	<i>Amblystoma</i> , <i>Bufo</i>	Rotation and rotated transplants—homeostatic and heterostatic	Anterior-posterior (AP) axis of otocysts becomes gradually fixed near the end of neurulation. The dorsal-ventral axis is fixed later and more abruptly. At time of fixation, reduplication can occur, around AP axis. Rotations after polarization may realign	STREETER (1907, 1914), SPEMANN (1910), OGAWA (1921, 1926), TOKURA (1924, 1925), HARRISON (1924, 1936a, b, 1945), CHOI (1931), HALL (1937, 1939, 1941), YNTEMA (1939, 1948, 1955), TRAMPUSCH (1941)
C. Proliferation of sensory and supporting cells of the Organ of Corti	Monkey— <i>Macaca</i> (25–39 days)	³ H-thymidine—short term	Cell division most intense in otocyst at 28–29 days, but continues in cochlear duct through 39th day	WILSON et al., (1975)

<p>Mice—CBA/J (embryonic-7 days postnatal); mutant mouse (11 days)</p>	<p>³H-thymidine—short- and long-term</p>	<p>Labelings of hair cells, Deiter's cells, Hensen's cells, ganglion cells and pillar cells on embryonic days 12-15; peak proliferation of all elements on day 14. Apical-to-basal proliferation gradient of cells of Organ of Corti; basal-to-apical gradient of ganglion cell proliferation. Cell cycle times</p>	<p>RUBEN (1967, 1973), RUBEN et al. (1971)</p>
<p>D. Differentiation of Organ of Corti</p> <p>Human (10-25 weeks)</p>	<p>Light microscopy of histological sections, EM, histochemistry</p>	<p>Timetables of histogenesis; basal-to-apical differentiation of inner hair cells prior to outer hair cells; Organ of Corti adult-like by 26 weeks; histochemical and cytochemical changes through 1 mo. postnatal</p>	<p>VAN DER STRICHT (1918, 1919, 1920a, b), ALEXANDER (1926), HELD (1926), KOLMER (1927), BAST and ANSON (1949), OMEROD (1960), WERSALL and FLOCH (1967), NAKAI (1970), MORGAN et al. (1971), YOKOH (1974)</p>
<p>Human (12-27 weeks)</p>	<p>Surface preparations</p>	<p>Earliest differentiation in middle of basal turn and proceeds in both directions; inner hair cells recognized prior to outer hair cells; quantification of hair cells at 3-6 mo</p>	<p>BREDBERG et al. (1965), BREDBERG (1967, 1968)</p>
<p>Sheep and goat (20-50 days)</p>	<p>Light microscopy</p>	<p>Timetable of normal development; basal-to-apical differentiation</p>	<p>TITOVA (1970)</p>
<p>Cat and dog (embryonic day 40-6 weeks postnatal)</p>	<p>Dissections (Retzius); light microscopy, scanning EM, and deaf mutant</p>	<p>Timetable of normal development; presence of kinocilia in newborn hair cells which degenerate later</p>	<p>RETZIUS (1884), PUJOL and MARTY (1968, 1970), PUJOL and HILDING (1973), BOSHER and HALLPIKE (1965), LINDEMAN et al. (1971), MAIR (1973)</p>
<p>Guinea pig (12-120 mm)</p>	<p>Light microscopy, histochemical, EM, surface preparations</p>	<p>Timetable of histogenesis and changes in PAS reaction, glycogen, RNA, DNA, Golgi bodies, lipids, alkaline phosphatase, acid phosphatase, succinate dehydrogenase, lactic dehydrogenase; basal-to-apical hair cell differentiation</p>	<p>VAN DER STRICHT (1918), CHONDYNIKI (1968), NAKAI and HILDING (1968), HILDING (1969), PUJOL and HILDING (1973)</p>

Tabelle 1 (continued)

Subject of study	Species (age)	Method(s)	Comments	Relevant references
	Rabbit (embryo-36 days postnatal)	Light microscopy, surface prepara- tions, EM, organ culture	Timetable of histogenesis; basal-to- apical differentiation; inner hair cells precede outer hair cells; adult- like at 18 days postnatal	BAGINSKY (1886, 1890), RETZIUS (1884), HELD (1909), WATERMAN (1938), ÄNGGÅRD (1965), NAKAI and HILDING (1968), HILDING (1969)
	Rat (embryonic to 45 months postnatal)	Light microscopy, surface prepara- tions, histochemical	Timetable of normal development, especially postnatal; quantitative changes in the cellular elements; basal- to-apical differentiation; inner hair cells precede outer hair cells; Na-K-activated ATPase activity increases rapidly during days 12-18; adult-like by 20-50 days postnatal	LANE (1917), VAN DER STRICHT (1918), WADA (1923), LORENTE DE NÓ (1926), BELANGER (1956), FALBE-HANSEN (1967), KUIJPERS (1974)
	Mouse (embryonic day 11-postnatal day 20)	Light microscopy, EM, ³ H-nucleic acid, autoradio- graphy	Timetable of normal development; basal-to-apical sequence may begin in middle of basal turn; inner hair cells differentiate earlier than outer hair cells; kinocilia in hair cells at birth disappear by 10 days; decreased RNA production during histogenesis; adult-like by 13-14 days postnatal	TELLO (1931-1932), LORENTE DE NÓ (1933a), OTIS and BRENT (1954), WEIBEL (1957), RAMON Y CAJAL (1965), MIKAELIAN and RUBEN (1965), KIKUCHI and HILDING (1965, 1966), ALFORD and RUBEN (1963), HILDING (1969), RUBEN (1969), SHER (1971)
	Mouse	Organ culture, mutants, irradiation	Histogenesis of sensory epithelium depends on association with rhomb- encephalon and on innervation by ganglion cells	GRUNBERG et al. (1940), HERTWIG (1942, 1944), DEOL (1956, 1964a, b, 1968), MIKAELIAN and RUBEN (1964), KIKUCHI and HILDING (1967), VAN DER BORDEN (1967), VAN DE WATER and RUBEN (1971, 1974), VAN DE WATER et al. (1973), RUBEN (1975)
	Hamster (embryonic to 20 days postnatal)	Light microscopy	Timetable of normal development, basal-to-apical sequence, adult-like at about 20 days postnatal	STEPHENS (1972), PUJOL et al. (1975)

Opossum (48-77 days postnatal)	Light microscopy	Middle of basal turn differentiates first; progresses in both directions	LARSELL et al. (1935, 1944)
Chicken (embryogenesis)	Light microscopy, organ culture (light and EM)	Timetables of normal development <i>in vivo</i> and <i>in vitro</i> ; basal-to-apical sequence of differentiation; role of innervation in hair cell differentiation; adult-like at 13-15 days; intracellular junctions during development of sensory elements	HOADLEY (1924), EVANS (1943), FELL (1928, 1929), FRIEDMANN (1956, 1959, 1969), PROCTOR and LAWRENCE (1959), FRIEDMANN and BIRD (1961, 1967), MCALPINE and FRIEDMANN (1963), VANZULLI and GARCIA-AUSTT (1963), REBOLLO and CASAS (1964), VAZQUEZ-NIN and SOTELO (1966), KNOWLTON (1967), ORR (1968, 1975)
Frog (9 mm to metamorphosis)	Light microscopy	Development of papilla amphiborium, lagena, and papilla basilaris	LARSELL (1934)
Mouse	³ H-thymidine	Basal-to-apical gradient of proliferation; peak proliferation on day 14	RUBEN (1967)
Human	Light microscopy	Divided opinion on placodal vs. neural crest origin; cells recognizable at 2.8-4 mm stage	STREETER (1906a, 1912), BARTELMER (1922), COOPER (1948), POLITZER (1956)
Rabbit, pig, sheep, cat	Light microscopy	Acoustic ganglia arise exclusively from placodal cells, splitting off from ventromedial wall of vesicle	VAN CAMPENHOUT (1935b), GROTH (1939), HALLEY (1955), BATTEN (1958)
Guinea pig	Light microscopy, histochemical sections	Placodal origin, cells migrate from rostral wall of vesicle	CHONDYCNICKI (1968)
Rat	Light microscopy	VII and VIII ganglia initially fused and of neural crest origin	ADELMAN (1925)
Mouse	Light microscopy, postnatal mutants	Correlated malformations of neural crest and organ of Corti; support crest contribution to ganglion	DEOL (1967, 1970)

E. Origin of ganglion cells

Proliferation

Origin

Table 1 (continued)

Subject of study	Species (age)	Method(s)	Comments	Relevant references
	Chicken	Light microscopy, organ culture, EM, transplantation, extirpation	Conflicting evidence regarding placodal or crest origin. Histological evidence suggests origin from ventromedial wall of otic cup at approximately 2 days. <i>In vitro</i> studies suggest crest origin	FELL (1928-1929), WADDINGTON (1937), PROCTOR and LAWRENCE (1959), REBOLLO and RODRIGUEZ (1964), PROCTOR and PROCTOR (1967), KNOWLTON (1967), VÁZQUEZ-NIN and SOTELO (1968), FRIEDMANN (1969), PARKS and ROBERTSON (1976)
	Amphibian	Light microscopy, extirpation, transplantations	Evidence strongly supports placodal origin	STREETER (1906b, 1907, 1909), BRACHET (1907), STONE (1922), KOSTIR (1924), TOKURA (1925), KNOUFF (1927, 1935), NIESSING (1932), RICHARDSON (1932), VAN CAMPENHOUT (1935a), YNTEMA (1937, 1939), KAAAN (1938), ZWILING (1941), WITSCHI (1949) TOERIEN (1965)
	Reptiles	Extirpation	Placodal origin assumed since extirpation of otic capsule eliminated ganglion cells	LANDACRE (1910), VEIT (1924)
	Fish	Light microscopy	Close proximity of otic cup and ganglion cells supports placodal origin	STREETER (1906a), COOPER (1948), BREDBERG (1968), NAKAI (1970), YOKOH (1971, 1974)
F. Innervation of hair cells	Human	EM, light microscopy	At 4½ weeks fibers appear to enter vesicle from ganglionic subdivision; at 6 weeks increased fiber outgrowth from ganglion cells; at 7½ weeks fibers from ganglion enter epithelium; basal-to-apical sequence of innervation; at 4 mo nerve fibers present in all turns; inner hair cells innervated before outer hair cells	

Cat	EM, light microscopy	30-day embryo axons seen entering organ of Corti; 58-day embryo afferent and efferent terminals present; innervation of inner hair cells precedes that of outer hair cells	RETZIUS (1884), WINDLE (1932a and b, 1933), PUJOL and HILDING (1973)
Rabbit	EM, light microscopy, explantation	Nerve fibers present before hair cells are recognizable; in 27-day embryo, afferent endings visible; 4 days postnatal, afferent and efferent endings abundant	WATERMAN (1938), NAKAI and HILDING (1968), HILDING (1969), PUJOL and HILDING (1973)
Guinea pig	EM and light microscopy	Innervation of hair cells probably begins around embryonic days 43-45; AChE and other enzymatic changes temporally correlated, basal-to-apical sequence. Afferent innervation precedes efferent	ROSSI (1961), CHONDYNIKI (1968), HILDING (1969), PUJOL and HILDING (1973)
Rat	Light microscopy	Nerve fibers present in organ of Corti in early (7-14 mm) embryo when hair cells first identifiable; hair cells innervated in 9-day neonate; innervation temporally correlated with hair cell and ganglion cell growth	LANE (1917), WADA (1923), LORENTE DE NO (1926, 1937)
Mouse	EM and light microscopy on normal and <i>in vitro</i> tissue, AChE histochemistry	Nerve fibers present during early otocyst differentiation (12-day embryo) and may influence hair cell differentiation; inner spiral bundle, last fiber system formed; synaptic contacts not present until 5-10 days after birth; basal-to-apical innervation; innervation of inner hair cells prior to outer hair cells; efferent endings present after afferents, just prior to function; afferent innervation correlates with formation of perilymphatic spaces; different AChE endings identifiable first at 7 days postnatal	HELD (1926), TELLO (1931-1932), LORENTE DE NO (1933a), RAMON Y CAJAL (1960), KIKUCHI and HILDING (1965), RUBEN (1967), DILLARD (1968), HILDING (1969), SHER (1971), VAN DE WATER and RUBEN (1971), VAN DE WATER et al. (1973), PUJOL and HILDING (1973), SOBKOWICZ et al. (1975), SCOTT (1967)

Table 1 (continued)

Subject of study	Species (age)	Method(s)	Comments	Relevant references
	Hamster	EM and light microscopy	At birth, afferent and efferent nerve fibers present; 2-3 days postnatal, terminals on hair cells; basal-to-apical sequence of innervation	STEPHENS (1972), PUJOL et al. (1975)
	Chicken	EM and light microscopy	Nerve fibers probably present soon after ganglion cell migration (3-4 days); innervation time not clear (see text); but by 10 days first terminals are apparent on basal hair cells; basal-to-apical sequence	BOK (1915), TELLO (1922), PROCTOR and LAWRENCE (1959), REBOLLO and RODRIGUEZ (1964), KNOWLTON (1967), PROCTOR and PROCTOR (1967), ORR (1968), VÁZQUEZ-NIN and SOTELO (1968), FRIEDMANN (1969)

^a Where original articles give size (crown-rump length), age in weeks was determined from AREY (1965).

^b Light microscopy refers to examination of histological sections from normal animals, with standard stains.

early appearance of axons, however, electron microscopic examination reveals that synaptic terminals are not present until just prior to cochlear function. In humans, synapses first appear in fetuses at 6—7 months, and in cats, afferent terminals are seen at about 58 days of gestation. The obvious question posed by this contrast is whether the peripheral processes of ganglion cells play some role in cochlear differentiation prior to synaptogenesis. The classic observation that these fibers may “wander” throughout the presumptive cell types of the developing organ suggested an inductive role, which recent studies have confirmed. That is, tissue culture studies on normal avian and mammalian otocysts, as well as *in vivo* and *in vitro* studies on mutant mice, all lead to the conclusion that some aspects of hair cell cytodifferentiation (e.g. formation of cilia) do not occur in the absence of cochlear nerve fibers. Furthermore, in areas where nerve fibers are absent, the morphology of the organ of Corti remains rudimentary. In this regard it may also be important to note that innervation of the organ of Corti occurs first in the basal turn and spreads predominantly apically, as described above, and that inner hair cells are innervated prior to outer hair cells. Finally, RUBEN (1967) has reported a basal-to-apical gradient of ganglion cell proliferation in the mouse. Taken together, and in relation to the differentiation gradients apparent in the organ of Corti, these observations strongly suggest that the ganglion cells may be providing a powerful regulatory and determinative influence upon cytological and morphological differentiation of the organ of Corti.

In addition to the terminals from the cochlear ganglion, hair cells of the organ of Corti receive efferent innervation *via* the crossed and uncrossed olivocochlear bundles. Early studies that concentrated on the presence or absence of nerve fibers did not discriminate between cochlear nerve and olivocochlear fibers, and recent histochemical attempts have met with the difficulty that early in development the ganglion cells, as well as efferents, stain positively for acetylcholinesterase (e.g. DILLARD, 1968). Extensive electron-microscope (EM) studies on a variety of mammals by HILDING and his colleagues (HILDING, 1969; SUGIURA and HILDING, 1970; PUJOL and HILDING, 1973) have shown that efferent terminals are formed after cochlear nerve terminals, and become apparent only slightly (1–2 days) prior to the onset of cochlear function.

II. Development of Central Auditory Pathways

The literature summarized in Table 2 deals with the ontogeny of neurons and their processes in the auditory pathways of the central nervous system. The table is organized by levels of the neuraxis. Within each level the author has attempted to find information on proliferation and migration, development of the soma, development of axonal and dendritic processes, development of synaptic terminals, ontogeny of interneuronal transmission, and where appropriate, myelination. In some cases large bodies of literature have been intentionally omitted, where the investigations were directed at a more general topic (e.g. cortical or thalamic development) and only studies where a primary concern was that for ontogeny of the auditory pathways have been included. In other cases, omission of

the classical literature was due to the difficulty in securing adequate translations. References dealing with central nervous system effects of early pathology or mutations of the inner ear have been largely omitted from this table; the reader is referred to the excellent paper by WEST and HARRISON (1973), which thoroughly summarizes the earlier work in this area, as well as presenting a thorough analysis of brainstem abnormalities in the deaf white cat. Finally, studies on the development of synaptic function which have utilized acoustic stimulation are included in Table 3 and discussed under the heading "Onset of auditory function" (Section B.III.).

The details of Table 2 are relatively self-explanatory. Thus this section only attempts to point out some of the general principles, areas of controversy, and areas in which more work seems especially desirable.

The interrelationships of functionally related neurons during ontogeny have been an area of continuing interest to developmental neurobiologists. However, relatively few studies have taken what might be called a "functional systems approach" toward studying the early ontogeny of the auditory pathways. Rather most investigations concentrate on a single nuclear region or on functionally unrelated parts of the brain (e.g. "ontogeny of the diencephalon"). Thus, the vast majority of investigations provide valuable descriptive information on the ontogeny of a particular region, but shed little light on the interrelationships between developing neurons. An examination of the body of literature cited in Table 2 reveals that for virtually every postproliferative phase of development, functional relationships between afferent fibers and their target cells have been hypothesized or conclusively demonstrated. Most modern investigations suggest that the migration of neurons to their final site is not influenced by their afferent innervation (JACOBSON, 1970). On the other hand, the investigations of LARSELL (1934) suggest that the cochlear nuclei in the frog are influenced by the incoming VIIIth nerve fibers during metamorphosis. In the opinion of this author, the matter is not completely closed. MOREST (1969a), suggests that afferent fibers could influence the final stages of nuclear migration within neurons of the medial trapezoid nucleus (see Section 3.2, below). In addition, we have recently acquired evidence that otocyst removal in the chick embryo will influence the final location of cells in *n. angularis* (PARKS and RUBEL, unpubl.). Unfortunately, current techniques for studying the position of proliferation and migratory routes of cells making up a single nuclear region do not allow adequate resolution of this problem. The development of more refined methods, such as isotope injections limited to a precise area of the neural tube, or refinements of genetic marking techniques, may alleviate this problem. With respect to other ontogenetic events, the results are much more convincing; cellular development, dendritic development, postsynaptic specializations, and myelination are probably influenced by afferent fibers and/or the electrical activity of the developing auditory system.

Probably the most pervasive result found in the literature on the ontogeny of synaptic transmission in central auditory pathways is that the primary central pathways are laid down and functional well in advance of cochlear function. This finding, first hypothesized by RAMON Y CAJAL (1960), has been repeatedly confirmed by anatomical and electrophysiological studies. On the other hand, it should not be hastily concluded that chemical or electrical communication

between cells is not involved in the establishment of these pathways; essentially nothing is known about the inherent electrical activity of the auditory system prior to the onset of cochlear function. Furthermore, some observations suggest that the early phases of pathway development may not be entirely independent of intercellular regulation. For example, several authors have noted that the first fibers to enter the medulla are from ganglion cells which will innervate the basal (earliest developing) portion of the cochlea. A similar developmental gradient is observed in both first- and second-order nuclei of the chicken brainstem. That is, the rostral (basal projection) areas of both nuclei precede the caudal parts in both cell death and cell growth (RUBEL et al., 1976). It is conceivable that these parallels between gross changes in the cochlea and brainstem nuclei are coincidental, but the findings again point to a need for more detailed studies of parallel developmental processes within functionally connected cell groups.

There are several topics about which little or no information is available on the ontogeny of auditory pathways. The most important of these have been noted above, namely the origin, proliferation, and migration of cells. Investigations on the proliferation and migration of the cochlear nuclei from the rhombic lip (His, 1890; PIERCE, 1967) stand as the exceptions; the cell groups have been carefully studied during their apparent migratory route. In addition, the "birthdate" (time of final mitotic cycle) has been established for several nuclei in a few species. However, it is becoming increasingly probable that cellular interactions at the lumen and during migration may be critical for understanding the ontogeny of neural networks. In lieu of new methods for studying these phenomena, the convergence of short-term ^3H -thymidine labeling, electron microscopic and Golgi methods may yield valuable hypotheses about the nature of such interactions. For example, we have previously suggested that cells in the brainstem auditory system may establish or specify their topographic connectivity during migration (RUBEL et al., 1976), and LAUDER and BLOOM (1976) suggest that connectivity may influence neuronal proliferation. Detailed studies of labeled neurons will establish the validity of these speculations.

Another area in which little information is currently available is the time at which cellular connections are established between post-migratory neurons within the auditory system. Such contacts may take two forms. On the one hand, a neuron projecting from, for example, the inferior colliculus to the medial geniculate body (MGB) may establish contact with the MGB cell but not form an excitable synapse. In this case, we have little access to either the time of establishment or the pattern of projections with current methods (but see CROSSLAND et al., 1975). On the other hand, at the time when synaptic connections are made, it is possible to identify the afferent projection by electrophysiological methods, and the concomitant changes in both presynaptic and postsynaptic processes by Golgi impregnation and electron microscopy. No single study has combined these methods, but PYSH (1969) has reported a two-fold increase in synaptic density with a large decrease in neuronal density in the inferior colliculus of rat, at a time when the oxidative metabolism dramatically increases and cochlear function begins. In addition, MOREST (1968, 1969a) utilized Golgi impregnations to give an elegant demonstration of an intimate correspondence between the temporal development of dendrites in the medial nucleus of the

Table 2. Development of central auditory pathways^a

Subject of study	Species	Comments	Relevant references
A. Cochlear nerve Myelination, growth of ganglion cells and their central axons	Human, cat, dog, rat, mouse, chicken	Myelination beginning at: human, 6 months; cat, 3-6 days before birth; dog, 3-8 days post- natal; rat, 5 days postnatal; mouse, 5 days postnatal; chicken, 12-day embryo. Myelination and axon diameter growth begin with fibers innervating basal turn and proceed toward apically innervating fibers. Ganglion cell growth and myelination correspond to nerve myelination. Full myelination prolonged	BECHTEREW (1885), WADA (1923), LORENTE DE NÓ (1926), LANGWORTHY (1933), RODRIGUEZ (1966), YAKOVLEV and LECOURS (1967), DILLARD (1968), FOX (1968a, b), PUJOL and MARTY (1970), WINDLE (1971), RAYMOND et al. (1976)
Cochlear root present in medulla	Human, cat, pig, hamster, chick	Human, 8-week embryo; cat, 11 mm; hamster, 6 days postnatal; chick, 5-day embryo	STREETER (1906a), BOK (1915), SHANER (1934), WINDLE and AUSTIN (1936), RAMON Y CAJAL (1960), RODRIGUEZ and REBOLLO (1966), STEPHENS (1972), RUBEL et al. (1976)
B. Rhombencephalon Origin and proliferation Examination of normal tissue	Human, pig, rat, mouse, chick	Most agree that cochlear nuclei arise from rhombic lip at a middle rostralcaudal level (<i>per contra</i> , Harmkark); site of origin of other auditory nuclei may be in ventral brainstem (cf. Cooper)	HIS (1890), MINOT (1892), BLAKE (1900), RAMON Y CAJAL (1908a, b), SHANER (1934), COOPER (1948), HARMKARK (1954)
³ H-thymidine	Mouse, chick	Proliferation of cochlear nuclei overlaps with period when nerve enters brain; no universal sequence regarding proliferation at primary, secondary and tertiary regions	PIERCE (1967, 1973), RUBEL et al. (1976), SMITH and RUBEL, unpubl.
Migration	Human, mouse, chick, frog	Some authors conclude that incoming acoustic fibers influence migration of cochlear nuclei; ordered "streaming" of the cells from rhombic lip is emphasized; otocyst removal has little influence on migration	HIS (1890), LARSELL (1934), SHANER (1934), LEVI-MONTALCINI (1949), KNOWLTON (1967), MILONYENI (1967), PIERCE (1968), RUBEL et al. (1976)

Differentiation Cellular	Human, pig, cat, mouse, chick, frog, salamander	Differentiation of primary and secondary nuclei appears to occur simultaneously. Final cell number influenced by afferents through regulation of cell death. Human brainstem nuclei apparent at about 6—7 weeks	RAMON Y CAJAL (1908a, b), FUSE (1913), BOK (1915), RICHARDSON (1932), LARSELL (1934), SHANER (1934), COOPER (1948), LEVI-MONTALCINI (1949), HALL (1964), RONRIGUEZ and REBOLLO (1966), K. NOWLTON (1967), MILONYENI (1967), RUBEL et al. (1976), PARKS and ROBERTSON (1976) <i>Chick</i>
Processes	Rabbit, rat, cat, opossum, chick	Axonal outgrowth precedes dendritic elaboration. Dendrites mature in temporal correspondence with attainment of afferent organization	BOK (1915), RAMON Y CAJAL (1960), MOREST (1968, 1969a, b), RUBEL et al. (1976)
Presynaptic terminals	Cat, rabbit opossum, chick	Reduced silver and Golgi preparations show elaboration of caliciform endings by progressive alteration of thin sinuous endings, in conjunction with dendritic and perikaryon maturation. No EM	MOREST (1968, 1969a, b), SCHWARTZ (1972)
Synaptic transmission	Rabbit, cat sheep	Electrical stimulation of cochlea or nerve prior to receptor function produces transmission to cortex in rabbit or cat. In sheep, middle ear reflex elicited prior to receptor function	MARTY and THOMAS (1963), MARTY and SHERRER (1964), MARTY (1967), PUJOL and MARTY (1968), MEYERSON (1967)
Myelination	Human, cat, dog, chick	Myelination in human begins around 6 months of gestation and follows sigmoid function; suggestion (LANGWORTHY) that myelination may be regulated by neuronal activity	TILNEY and CASAMAJOR (1924), LANGWORTHY (1933), RODRIGUEZ and REBOLLO (1967), YAKOVLEV and LECOURS (1967), FOX (1968b), SCHWARTZ (1972)
C. Mesencephalon Origin and proliferation	Mice, chick	In mice, proliferation of neurons in inferior colliculus and nuclei of lateral lemniscus overlaps with proliferation of cochlear and olivary nuclei cells	PIERCE (1973), KARTEN, unpubl.
Differentiation Cellular	Rat	Cell density in inferior colliculus decreases markedly during days 1—14 postnatal	PYSH (1969)
Processes	Human, rat, rabbit, guinea pig, opossum	Dendrites in inferior colliculus present well before onset of function; dendritic development in central nucleus precedes that in superficial layers. Extracellular space decreases around onset of hearing while monoamine oxidase activity increases	COOPER (1948), WAWRZYNIAK (1966), MOREST (1969b), PYSH (1969)

Table 2 (continued)

Subject of study	Species	Comments	Relevant references
Presynaptic terminals	Rat	Synaptic profiles present at birth in the rat; two-fold increase in density of profiles between 1 and 14 days	Pysh (1969)
Synaptic transmission	Cat, rabbit	Present at birth in both species	MARTY and SCHERRER (1964), MARTY (1967), PUJOL and MARTY (1968)
Myelination	Human, cat, dog	Beginning around 6 months' gestation in human, and birth in cat and dog	TILNEY and CASAMAJOR (1924), LANGWORTHY (1933), YAKOVLEV and LECOURS (1967), FOX (1968b)
D. Diencephalon (Medial geniculate)			
Origin, proliferation, and migration	Human, rabbit, rat, mouse, chicken	Alar plate origin as part of dorsal thalamic region; follows migration of ventral thalamus. First identification in humans at about 10 weeks, anlagen recognized at 8½ weeks. First neurons formed in dorsal thalamus; rat—days 14 and 15; hamster—days 16–18	HIS (1890, 1904), CLARK (1933), MUIRA (1933), GILBERT (1935), KUHNENBECK (1964), ROSE (1942), COOPER (1948), DEKABAN (1954), STRÖER (1956), NIMI et al. (1962), COGGESHALL (1964), KEYSER (1972), MCALLISTER and DAS (1977)
Differentiation			
Cellular	Human	At six months, cells are small and multipolar	COOPER (1948)
Processes	Cat	Dendritic development completed between birth and end of second week; principal division differentiates prior to dorsal division	MOREST (1964)
Synaptic transmission	Dog, cat, rabbit	Synaptic transmission at birth as shown by potentials at cortex from stimulation of 8th nerve or inferior colliculus	MARTY and SCHERRER (1964), MARTY (1967), MYSLIVECEK (1968), PUJOL and MARTY (1968)
Myelination	Human	Begins during 7th month of gestation; among earliest thalamic fibers to become myelinated	LANGWORTHY (1933), YAKOVLEV and LECOURS (1967)

A. Telencephalon (Auditory cortex) Differentiation Cellular	Human, mouse	Decreasing neuron density and increasing size in human between 8-month fetus and 4-year-old child; especially before term. In mice, some changes during first postnatal month	CONEL (1939-1963), RABINOWICZ (1964, 1967), GYLLENSTEN et al. (1966)
Processes	Dog, human	In the dog, Layer-V pyramidal cells have apical and basal dendrites at birth; in smaller pyramidal cells of Layers-II and -III basal dendrites develop postnatally; rapid period of dendritic growth between 14 and 30 days postnatal. In human, massive dendritic expansion after 8th prenatal month	CONEL (1939-1963), RABINOWICZ (1964, 1967), FOX (1968a, b)
Presynaptic terminals	Rat	First synapses apparent on day 16 of gestation; axodendritic on "newly arrived" cells in marginal layer; axosomatic synapses apparent on day 18	KÖNIG et al. (1975)
Synaptic transmission	Cat, rabbit, rat, guinea pig, dog	At birth, evoked potentials recorded in ipsilateral and contralateral primary and secondary auditory regions, claustrum and contralateral MGB upon stimulation of medial geniculate body; 2-3 times adult latency; following rate restricted and little augmentation	MARTY and SCHERRER (1964), HASSMANNOVA and MYSLIVECEK (1967), MARTY (1967), CHALOUPKA et al. (1968), HASSMANNOVA et al. (1968), MYSLIVECEK (1968), PUJOL and MARTY (1968)
Myelination	Human, dog, cat	Thalamocortical fiber myelination occurs gradually during postnatal period; correlates with evoked potential latency decrease	LANGWORTHY (1933), MARTY and SCHERRER (1964), YAKOVLEV and LECOURS (1967), FOX (1968a, b)

^a This table does not include studies that utilized acoustic stimulation (see Table 3: Functional development).

trapezoid body and the arrival of afferent axons. Aside from these examples, there are virtually no detailed investigations of the ontogeny of projections onto cells of the auditory pathway. Coupled with the paucity of knowledge on neurochemistry and its development in the central auditory pathway, these omissions make it impossible to state the temporal contingencies that occur during normal auditory system development.

Two final areas that should receive increased attention are: i) the development of centrifugal projections within the brain; and ii) the ontogeny of topographical specificity. The former has received little attention in any sensory system, and probably plays a critical role in the ontogeny of mature function. The topic of specificity, on the other hand, has received a great deal of attention in the visual system (see Chapters by HIRSCH and LEVENTHAL and BATE). Since the concepts stemming from the work on the visual system could be examined and extended by considerations of the tonotopic and binaural representations in the auditory pathways, it is hoped that future research will be directed at this problem.

III. Development of Auditory Function

The functional characteristics of the auditory system can be assessed by physiological and behavioral means; each has advantages and disadvantages. The readily available microelectrode and macroelectrode methods make it possible to analyze the functional capacity of different parts of the system in such a way as to answer such questions as the following: is the system functional, i.e. does it respond to sound? what frequencies elicit responses? are the changes in relative sensitivity over age? and do changes in frequency of amplitude sensitivity relate to morphological changes in the peripheral or central auditory pathways? More recently a number of laboratories have begun to investigate the ontogeny of "coding properties" of cells within the auditory system, presumably in order to relate properties such as tuning curves, phase locking, or response profiles to the ontogeny of behavioral capacities. Unfortunately, in no case is it clear what specific properties of unit response functions are related to any behavioral capacity, and clear examples of units responding as species-specific "feature detectors" have not been established (CAPRANICA, 1977). Therefore, although studies of unit coding characteristics are of interest for understanding nervous system ontogeny, the results should not be considered indicative of an organism's ability to respond selectively to meaningful environmental acoustic differences. Behavioral investigations of the ontogeny of auditory function, on the other hand, can provide information regarding an animal's minimum perceptual abilities. However, behavioral studies rely on a set of assumptions that are often difficult to meet. These include: i) That there is no ontogenetic change in the sensitivity of the response measure or unconditioned S-R chain; ii) That the topography of the response remains stable over time; and iii) That an organism's sensory capacities are somehow tied to the motor system in such a way as to be able to generate differential responses. Since these requirements can almost never be fully assumed

when dealing with a developing system, negative results from behavioral studies cannot usually be interpreted. Furthermore, because a stable response measure is difficult to find, large numbers of subjects are usually required and adequate control procedures or populations are essential. Taken together, these factors often make behavioral studies of sensory ontogenesis more difficult to undertake, and more open to criticism, than physiological investigations. Yet, in the final analysis, we are concerned with understanding the ontogeny of a system (audition) with which the animal can make meaningful interpretations regarding its environment, leading to differential behavioral outcomes. Thus, behavioral investigations using carefully chosen response measures, adequate controls, and sufficiently powerful analytical tools, are of the utmost importance.

In Table 3, studies of functional development are subdivided by species and major response measures. Although this table is primarily intended to summarize the state of knowledge on the onset of auditory function, studies of functional development which focus on more complex auditory processing have also been included. Thus, investigations of cellular response parameters, behavioral differentiation of acoustical properties, conditioning, and perception of species-typical vocalizations are also included. Earlier reviews by GOTTLIEB (1968b, 1971b) on the onset of sensory function, BRADLEY and MISTRETTA (1975) on fetal receptor development, and TEES (1976) were helpful in compiling the bibliography. As earlier, there are several areas that are not covered fully in the table. First, most of the literature on human behavioral development with respect to postnatal auditory and language function has not been included, since postnatal development of human auditory function is thoroughly reviewed by EISENBERG (1976), and there are a number of recent texts on language development. Second, the voluminous literature on human cortical evoked potentials has not been fully covered, but the important findings are believed to have been noted and the references cited provide access to the relevant literature. Third, the excellent work of RUBEN and his colleagues on the development of auditory function and its degeneration in mutant mice is not included (MIKAELIAN and RUBEN, 1964, 1965; MIKAELIAN et al., 1974; BROWN and RUBEN, 1969). As above, discussion of Table 3 will be limited to the important principles, controversies, and questions for future research.

1. Onset of Cochlear Function

One primary goal of research on the ontogeny of auditory function, whether physiological or behavioral, is to identify the relationships between structure and function. The general problem of identifying structure-function relationships is central to all life sciences; ontogeny would seem to be an unusually powerful approach, since parallel ontogenetic changes in structure and function can be investigated. Thus a large number of investigators have attempted to determine "the final morphogenetic event" leading to the establishment of cochlear function by studying cochlear morphology in parallel with either physiological or behavioral indices of functional activity. It should be noted that freeing of the tectorial membrane, development of the *stria vascularis* and associated endocochlear potentials, formation of afferent terminals, formation of efferent terminals, and

other aspects of cochlear development have all, at one time or another, been cited as *the* final factor initiating cochlear function. Most investigators seem to prefer giving credit to some sort of neural innervation change, but a minority also propose biochemical changes or morphogenetic changes in hair cells or supporting elements of the organ of Corti. In point of fact, the single most common observation throughout this literature is that simultaneously with the onset of cochlear function, the inner spiral sulcus forms by the regression and/or degeneration of pseudostratified epithelium. This and other changes can be clearly seen in the reproduction of RETZIUS's illustration of cochlear development of the cat (Fig. 2). Various investigators (e.g. BAST and ANSON, 1949; ÄNGGÅRD, 1965; PUJOL and HILDING, 1973) have recognized the probable importance of this event for allowing a shearing force to be set up between the tectorial membrane and the hair cell cilia. Without this sulcus (see Fig. 3) movement of the basilar membrane would not be converted to transverse rocking movements of the organ of Corti, which presumably generate the "adequate stimulus" for hair cell ionic fluctuations.

Although formation of the inner spiral sulcus is of great importance for the establishment of cochlear function, it is probable that neither it nor any of the other events noted above is uniquely responsible for the onset of hearing. As part of his study on the ontogeny of the rat cochlea, which stands as the most thorough investigation of cochlear ontogeny to date, WADA (1923) compared the cochleas of rats that "reacted to a shrill whistle or handclap" with those of littermates that did not respond. He concluded that "the inception of hearing does not coincide with detachment of the tectorial membrane from the papilla spiralis, but with the development of *each constituent* of the papilla spiralis and the membrane tectoria" (my emphasis) (p. 154). Over half a century later this conclusion still holds; contrary to the notion of a single developmental event that initiates functional integrity, there seems to be some sort of autoregulation, such that simultaneous growth and destruction of constituent cell types leads to a cochlea that is electrically, chemically, and mechanically capable of rudimentary function. And then, quite rapidly, the cochlea attains a maturity that cannot be distinguished from adults of the species. It is not clear whether a single causative agent exists, or each element develops independently, or whether there is a form of autoregulation that synchronizes all elements (through their oxidative metabolism or some other process). However, the last idea should not be hastily discarded. It is now known that coinciding with the ontogenetic events leading to and immediately following functional onset of the organ of Corti, there are corresponding changes in functionally related tissues, such as the maturation of Reissner's membrane, rapid maturation of the *stria vascularis* and concomitant development of the endocochlear potential, growth of spiral ganglion cells, and maturation of central nervous system elements. Not only is there synchrony in the time of occurrence of morphological and chemical changes leading to functional integrity, but the ensuing changes with respect to the *pattern of development* in the cochlea and central nervous system structures presents a similar parallel. The basal-to-apical changes in cochlear development are coincident with rostral-to-caudal changes observed in the medullary nuclei of the chick embryo (RUBEL et al., 1976); basal portions of the cochlea are represented in rostral portions of these brain stem nuclei, and apical (or distal) regions project to caudo-lateral sites (see Section 3).

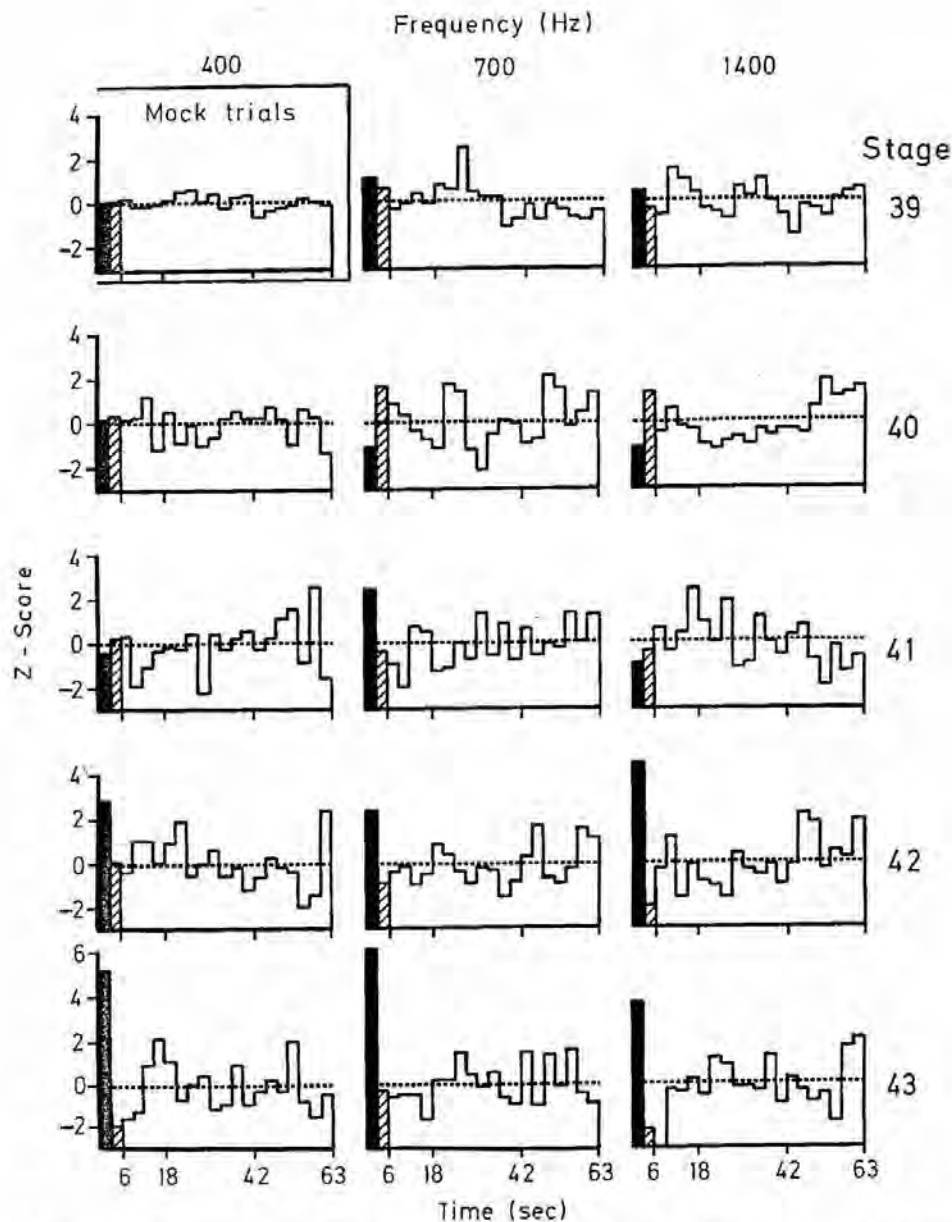


Fig. 6. Each histogram shows normalized activity scores of 12–17 chicken embryos in response to acoustic stimulation. Embryonic stage (HAMBURGER and HAMILTON, 1951) at which subjects were tested are indicated along right margin, frequency of acoustic stimulus along top. Each embryo tested at one age with one frequency. Five trials were presented (5 min apart). In each trial, stimulus was presented (115 dB, SPL) for 3 s (black bar) and activity was electronically recorded for each 3-s period from stimulus onset for succeeding 63 s. Shaded bar indicates immediate poststimulus period. Positive Z-scores indicate increase in activity over baseline, and negative Z-scores indicate inhibition of activity. “Mock” trials are nonstimulus trials; flat histogram indicates no recording artifact. At stage 40 (14–15 days) statistically reliable inhibition of motility was found in response to 700-Hz and 1400-Hz stimulus. At stage 41 (15–16 days) reliable increase in motility was recorded to 700-Hz stimulus. At stages 42 and 43 (16–18 days) all stimuli evoked increased activity. (From JACKSON and RUBEL, 1978)

Any considerations of the time at which cochlear function begins must take note of the species variability. Whereas GOTTLIEB (1971b) paid specific attention to the overwhelming similarity in the sequence of sensory system maturation in birds and mammals (i.e. tactile-vestibular-auditory-visual), little is known regarding why particular systems become functional when they do. Obviously it can be asserted

that there is some selective advantage brought to bear, or that it is merely coincident with the age and developmental state at which partition or hatching occurs. However, these "explanations" add little to our understanding of what particular selective advantage is accrued. In precocial birds, the auditory system becomes functional, as defined by electrophysiological or behavioral measures, well before hatching. For example, chick embryos will demonstrate a cochlear microphonic or brainstem evoked potential response on day 12 or 13, and as shown in Fig. 6, behavioral responses can be elicited by acoustic stimulation of the intact egg on day 14–15 (Stage 40). While it has been shown in some avian species, and implicated for others, that parent- or sibling-produced sounds have a function in regulating hatching or post-hatching behavior, such claims only appear to concern the last two or three days prior to hatching. Thus, it is not at all clear why the auditory system of the chick or duckling becomes capable of function 6–8 days before hatching, much less why the human auditory system is functional around 30 weeks of gestation. Such early function may be a mere coincidence of developmental stage at parturition. On the other hand, it is important to consider two additional possibilities. First, it is conceivable that in order for the system to be capable of appropriate functioning at the period of development where it will first be utilized for signal analysis, extrinsic input from the external or internal environment is actually being processed near the time functional activity can first be elicited in the laboratory. Second, as suggested by GOTTLIEB (1971a, b), it is also possible that functional activity intrinsic to the auditory system itself is somehow regulating its development. In this case, the fact that function can be elicited in unusual laboratory conditions may be merely an epiphenomenon.

2. Ontogenetic Changes in Stimulus Parameters

In addition to considering the time at which the auditory system first becomes functional, it is important to consider the stimulus parameters which will first elicit a response. In Table 3, these parameters (when available) are briefly noted in the fourth column. While it is clear that responses can be elicited at decreasing stimulus intensities and increasing repetition rates as the animal matures, these parameters will not be discussed. Of more interest are the ontogenetic changes in frequency parameters adequate to evoke a behavioral or physiological response.

Perusal of Table 3 indicates that in virtually every animal in which an adequate range of frequencies has been used, responses can first be elicited by low to low-middle frequency tones. Thus, in the human fetus, the tonal frequencies that first elicit changes in heart rate or motility are in the 500–1500 Hz range. This problem has been most extensively investigated in cat, where MARTY and his colleagues have systematically investigated evoked potentials and cellular responses throughout the auditory system. Thus, information is available regarding onset of responses from the cochlea and from each major nucleus along the central auditory pathways, and behavioral responses to sound. Although the evidence is somewhat conflicting, in that the first cochlear microphonic (CM) and behavioral responses are to frequencies under 1 kHz, while evoked potential and unit responses are to tones in the 0.5 to 2.0 kHz range, all studies agree that responses

to frequencies above 2.5 kHz are relatively delayed in comparison with low frequency tones. Similar results (i.e. low or low-to-middle frequencies elicit responses prior to high frequencies) have been found in most mammals and birds where adequate testing has been conducted, and in every reported study the extreme high frequencies for the species in question are the last to reliably elicit a response.

It is now well known that in birds and mammals, apical portions of the basilar membrane respond maximally to low frequencies while basilar portions are most responsive to high frequencies (BEKESY, 1960; DALLOS, 1973). Therefore, if cochlear differentiation and functional development were to correspond, an apical-to-basal differentiation gradient would be predicted for the mammalian organ of Corti and avian basilar papilla. As stressed earlier, however, studies of peripheral differentiation have shown the opposite result. That is, differentiation of the hair cells, innervation of the hair cells, development of the spaces of Nuel, opening of the tunnel of Corti, formation of the inner spiral sulcus, differentiation of the *stria vascularis*, etc., all occur first in the basal or mid-basal turn of the cochlea and last at the apex. Thus there appears to be a dissociation between the ontogeny of functional responses to tonal stimuli and the differentiation of the cochlea. Several suggestions have been put forward to resolve this apparent paradox. FOSS and FLOTTORP (1974) examined the ontogeny of startle responses of cats, rabbits, dogs, and mink to pure tones of 125 Hz to 8 kHz, and consistently found that initial responses were elicited by tones under 1.0 kHz. Based on observations of the locations of the major blood vessels in the *mature* human ear, they concluded that the upper portion of the basal coil and lower portion of the second coil probably receive an adequate blood supply earliest, and that the frequencies represented at those locations are the first to elicit a response. Thus they contend that a dissociation does not exist and that functional ontogeny of the cochlea and corresponding frequency responses are governed by the developing circulatory system. This view, however, ignores the fact that high-frequency responses are the *last* to mature, while in the cochlea, differentiation of the *apical* turn is delayed. Furthermore, their own observation that little is known about the ontogeny of the cochlear vasculature, coupled with the fact that it most probably correlates with the general gradient discussed above, compels this author to accept the dissociation and consider alternative explanations.

SAUNDERS et al. (1973, 1974) observed that the ability to record high-threshold brainstem-evoked potentials to frequencies above 1.3 kHz in chick embryos corresponds to the embryo's entrance into the air space of the egg and the subsequent cavitation of the middle ear. These authors hypothesized that the mesenchymal tissue of the immature middle ear may cause an impedance mismatch leading to selective attenuation of high-frequency stimuli. Careful inspection of their data, however, reveals that cavitation of the middle ear corresponded with a 20–30 dB increase in sensitivity, which was uniform across the 0.1–3.0 kHz range that could be considered. In addition, other indications of the effects of middle ear loading (e.g. WEBSTER, 1962; FOSS and FLOTTORP, 1974) and direct measurements of impedance (ROBERTSON et al., 1968; KEITH, 1975) suggest that attenuation due to middle ear loading would be approximately uniform across the audible frequency range. On the other hand, in the one study that

bypassed the middle ear by direct acoustic stimulation of the oval window in neonatal rabbits, ÄNGGÅRD (1965) reported that the earliest cochlear microphonic potentials could be elicited by stimuli in the 2–4 kHz range. Two days later CMs were observed over the entire 0.2–10 kHz range used and there was a uniform threshold reduction of 30–35 dB over the succeeding 20 days. Since no comparable data exist on the ontogeny of CMs in rabbits with intact middle ears, it is not possible to draw conclusions about differential middle ear attenuation during ontogeny. It will be important, however, for future investigators to compare response functions obtained by tonal stimulation of the intact ear with those obtained by direct stimulation of the oval window.

A second explanation of the apparent dissociation between the morphological development of the cochlea and the ontogeny of physiological and behavioral responses has been reiterated (RUBEL et al., 1976). We suggested that the developing cochlea is indeed first responsive to sound in the region which is most mature, i.e. near the middle of the basal turn in mammals and toward the basal one-third in birds. However, the transduction properties of the immature cochlea are probably not identical with those of the adult, and factors such as the greater mass per unit area due to the immaturity of the organ of Corti, basilar membrane, and inner spiral sulcus would cause an inertial load restricting the frequency following of the basilar membrane to low frequencies and tending to damp the displacement of the traveling wave. Thus, we have proposed that in the immature animal the basilar portion of the cochlea is the first to transduce mechanical vibrations into neural signals, but that due to its immaturity (probably less tension on the basilar membrane and/or greater cellular density of the basilar membrane and organ of Corti) its response is primarily to low frequencies. In this case, sound transduction in the cochlea would commence toward the basal region in response to low frequencies and progress first in both directions, and then apically. Concurrently, there would be an increase in the ability to transduce successively higher frequencies at the rapidly maturing basal end of the cochlea, while progressively more apical regions would mature to the stage where responses to low frequencies would be initiated (note that in the mature cochlea the basal region responds to both low and high frequencies, while the apical region responds only to low frequencies). Although our suggestion is slightly more detailed, several previous authors (e.g. LARSELL et al., 1944; VANZULLI and GARCIA-AUSTT, 1963; PUJOL and MARTY, 1970) have suggested that ontogenetic changes in the mechanics of the cochlear partition are responsible for the discrepancy between cochlear ontogeny and functional responses. In addition to its accordance with the morphological observations on cochlear development, this hypothesis gains some support from observations on central nervous system ontogeny. First, we have recently shown (RUBEL et al., 1976) that the differentiation of 2nd- and 3rd-order auditory regions in the chicken brainstem proceeds in a spatial direction which corresponds to the basal-to-apical pattern observed in the cochlea. That is, normal histogenic cell death, volumetric changes, and qualitative signs of differentiation all occur initially in the rostral end of each nucleus, which receives projections from the basal portion of the cochlea and responds to relatively high frequencies in the mature system (RUBEL and PARKS, 1975). The caudal (or apical projection) regions, which respond to low frequencies in the adult, are relatively delayed in

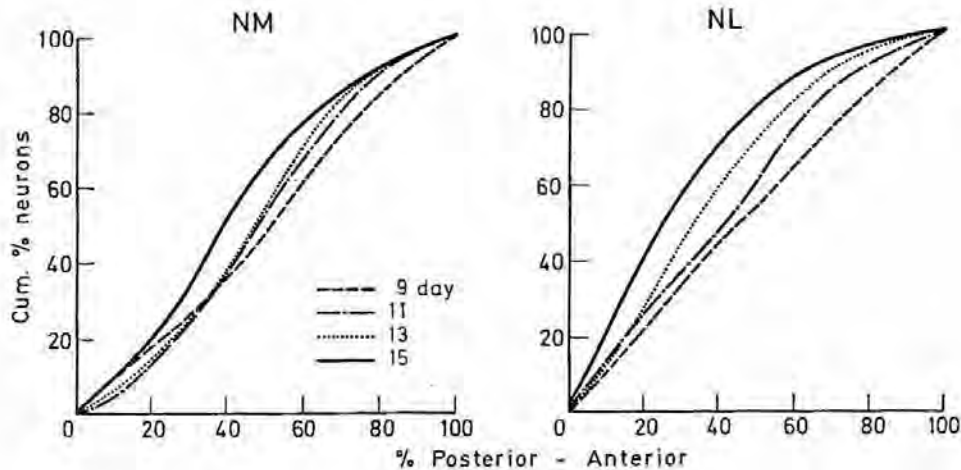


Fig. 7. Spatial distribution of cell numbers in *n. magnocellularis* and *n. laminaris*, across age. To compensate for varying rostrocaudal dimensions of nuclei at different ages, total extent of nuclei is represented in terms of cumulative percentages of distance from posterior to anterior end. Similarly, to compensate for differing numbers of cells at different ages, number of cells is expressed in terms of cumulative percentages of totals at each age. In particular, note increases in initial slope (at posterior end) and decreases in final slope (at anterior end) for both nuclei at successively older ages, indicating systematic shift in relative numbers of cells from anterior portion of each nucleus toward posterior regions. NM, *n. magnocellularis*; NL, *n. laminaris*. (From RUBEL et al., 1976)

their differentiation. This rostral-to-caudal gradient for cell death in *n. magnocellularis* (2nd-order neurons) and *n. laminaris* (3rd-order neurons) is shown in Fig. 7. At day 9 of embryogenesis, the distribution of neurons over the rostral-caudal extent of each nucleus is relatively uniform. By 11 days, this distribution deviates from uniformity at the rostral end, where cell loss has begun. During the following four days (11–15) cell loss occurs at successively more caudal locations, causing the deviation from uniformity (45° line on graphs) to occur at points successively more toward the caudal end. Similar changes occur when nuclear volumes are analyzed and, as noted, for a number of qualitative indices.

If neural activity or some other aspect of afferent input influences these developmental parameters, which it almost certainly does (see Section C. III), this gradient suggests that the neurons in the basal projection regions are the first to receive afferent input, with apical projection regions becoming functional at successively later times. This scheme would also explain the results reported by PUJOL and MARTY (1968). Recording evoked potentials from the primary auditory region (A1) of the feline cerebral cortex 2–3 days after birth, they found responses only to low-to-middle frequencies. More importantly, potentials were localized toward the *rostral portion* of the middle ectosylvian gyrus, which receives projections from the base of the cochlea and which responds maximally to high frequency tones in the adult cat. This finding does not rule out the possibility that high frequencies are selectively attenuated by the immature middle ear. It does suggest, however, that in very young kittens, the basal region of the cochlea is responding to low-frequency stimuli and that the apex is unresponsive to low frequencies, especially in view of the fact that at birth electrical stimulation of the auditory nerve evokes responses throughout the primary auditory projection area.

A final resolution of the factors influencing the development of frequency resolution in the developing cochlea is fundamental for an understanding of

normal ontogeny of audition as well as for consideration of the role of experience in the development of the central auditory pathways. In this regard it is interesting to note that low- to middle-frequency sounds predominate in the embryonic environment of mammals and birds. High frequencies are poorly represented endogenously in the intrauterine environment and exogenous high frequencies are attenuated more than lows by the abdominal wall of mammals (see Table 4) and by the eggshell in birds (JACKSON and RUBEL, unpubl.). Since the tonotopic organization of primary auditory regions of the brain have now been described for many mammalian species and quantitative "maps" are available for the brainstem nuclei of the chicken, it should be possible to resolve any ontogenetic changes in frequency representation. One method would be to correlate unit electrophysiological responses to properties with position of the responding neural elements. Another, more exciting, possibility would be to apply recently developed "metabolic" methods such as labeled 2-deoxyglucose autoradiography (KENNEDY et al., 1975). Application of this last-named method to problems of functional development, in general, offers the exciting prospect that stimulation can be applied to an intact organism in its otherwise normal sensory environment.

3. Ontogeny along the Neuraxis

As implied earlier, very little can be said about the particular morphogenetic events responsible for functional changes in the cochlea or central auditory pathways. The cochlear microphonic potential onset correlates with the appearance of a positive increase in amplitude of the endocochlear potential, and a negative summing potential (DC shift in response to stimulation) recorded in the scala media (ÄNGGÅRD, 1965). The summing potential reverses polarity, to become positive, at about 15 days postpartum in the rabbit, which suggests that it may be related to the later innervation of the outer, as opposed to inner, hair cells. However, anatomical confirmation that the time of innervation correlates with this polarity shift has not been forthcoming.

In species where both CMs and nerve potentials have been examined, the onset of responses attributable to VIIIth nerve action potentials seems to lag behind onset of the cochlear microphonic by a day or two (see PUJOL and HILDING, 1973). In the mouse it appears that nerve potentials recorded directly from the VIIIth nerve lag behind those recorded from the round window as well. It is not at all clear why these differences should occur. They may represent differences in recording sensitivity, or real dissociations between the functional elements initiating the various potentials. In any case, no morphological changes have been identified that account for them.

Concurrently with the onset of cochlear and nerve potentials, evoked potentials can be recorded throughout the primary auditory pathways. The onset and elaboration of these evoked potentials have been extensively described for most laboratory animals and for humans. Excellent reviews are available on both human (HECOX, 1975; EISENBERG, 1976) and animal studies (ROSE and ELLINGSON, 1970; MYSLIVEČEK, 1970; SCHERRER et al., 1970). In addition to showing the ages at which the evoked potentials are first elicited by a click or pure tone stimulus, these studies can be summarized as follows: i) Evoked potentials increase in

amplitude with age, which is probably due to recruitment of more elements responding to a stimulus of a given magnitude; ii) Thresholds decrease with age, probably indicating mechanical or neural changes in the cochlea and peripheral structures, increased ramification of neural processes, and, tentatively, changes in the efficiency of individual synapses; iii) Latencies of responses decrease markedly during the first two weeks of function and more slowly thereafter, which initially is attributable to growth and myelination of peripheral axons, and then decreases in central transmission time; iv) Increased ability to follow repetitive stimuli, which may be attributed to the development of recurrent inhibitory mechanisms, changes in transmitter availability, or changes in the ionic compartmentalization capacities of the cells; v) Increased recruitment (i.e. augmentation of response) with low frequency stimulation; vi) Increased complexity of evoked potentials (especially cortical), with immature responses being dominated by the negative component, and then the initial positivity as well as later waves maturing.

Little advance has been made in identifying specific neuronal changes responsible for the various aspects of evoked potential maturation in the auditory system. However, some progress has been made in determining the location(s) of such changes. For example, by recording responses in the medial geniculate nucleus and the auditory cortex, ROSE et al. (1957) were able to establish that the latency reductions were primarily of subcortical origin, rather than in the thalamocortical relay. Similarly, a series of studies on human neonates (see HECOX, 1975) has extrapolated from the waveform identification available on adults to determine that the initial latency change seen in human neonates is in VIIIth nerve transmission time. The extensive series of investigations by the Czechoslovakian group (see MYSLIVEČEK, 1970) is a further example; by using regional stimulation and cortical recording, they have been able to delimit the sites of several ontogenetic changes to either peripheral components or central neural networks. By far the most systematic investigation of the ontogeny of auditory evoked responses from the central nervous system has come from the French group (see MARTY, 1962, 1967; PUJOL, 1972). This series of investigations has established that i) Responses are obtained simultaneously 2-3 days postnatally in kittens in all central nuclei of the primary auditory pathways; ii) The latency decreases occur at successively higher levels of the neuraxis; iii) Responses are elicited by tones (at least three sinusoidal periods) before responses are obtained to clicks; iv) The topography of acoustically-driven synaptic connections in the cortex may be altered during the first postnatal week due to the loss of thalamic inputs to superficial cortical layers (KÖNIG et al., 1972); and v) Auditory responses are seen in association areas of the cerebral cortex concurrently (at 2-3 days in the kitten) with primary responses. With respect to the last finding it is interesting to note that responses to click stimuli were not reliably recorded in the kitten cerebellum until *several weeks* after birth (SHOFER et al., 1969).

4. Neuronal Coding of Pure Tones

In contrast to the plethora of information on evoked potential maturation, there is a relative paucity of data on the response contingencies (stimulus coding) of individual neurons during auditory system maturation. Undoubtedly, one

reason that little attention has been directed toward this area is that neurons in which the response contingencies are congruent with particular environmental features ("feature detectors") have been less evident in the auditory than in the visual system. As confidence dwindles in the heuristic value of a model asserting the necessity of hierarchically organized feature construction, it may become apparent that the ability to parametrically control the attributes of acoustic signals will be highly advantageous for understanding the ontogeny of information processing in the brain.

The coding properties of neurons can be defined with respect to either the stimulus properties that reliably elicit an extracellularly recorded neuronal response (either increase or decrease in number of action potentials over time) or the response characteristics themselves. One fundamental form of coding is the tonotopic organization of neurons found within each nuclear region: the characteristic frequency (CF), or lowest threshold excitatory frequency, of neurons within a nuclear region is systematically distributed across the nuclear region. The tonotopic organization undoubtedly results from the sequential spatial organization of the cochlea and topographic projection of each neural region onto its target population. Tonotopic organization is apparent as early as neuronal responses to stimulation can be elicited from the central nervous system (PUJOL and MARTY, 1968; KONISHI, 1973; AITKIN and MOORE, 1975). At the present time, it is not possible to make a definite statement as to the extent of the neural region that is occupied by neurons responsive to auditory stimulation at the early ages, and there is reason to believe that the region responsive to a given frequency may shift during development.

Less developmental work has focused on more complex coding parameters, such as two-tone interactions, tuning curves, response areas, phase locking, response types, and binaural interactions. Since these are critically important considerations for future investigations, the ontogenetic information that is available on each will be briefly described.

a) Two-tone interactions, typically where the cellular response to one tone is inhibited by the addition of another frequency, have not been studied developmentally.

b) Tuning curves indicate the excitatory thresholds of a unit at frequencies surrounding the characteristic frequency (CF) for that cell. A tuning curve typically consists of a U- or V-shaped function, which indicates the frequency specificity of the excitatory response. KIANG et al. (1965) introduced the use of a quantitative measure ("Q") of the sharpness of tuning ($Q = \text{characteristic frequency} / \text{bandwidth } 10 \text{ db above excitatory threshold}$). The Q measure is in direct proportion to the sharpness of tuning (slope of the tuning curve). There are several reasons to suspect that tuning curves may become sharper during the early stages of auditory function. First, the general view of embryonic canalization suggests not only that tissues become increasingly determined, but also that physiological and behavioral processes might become increasingly specific during development (WADDINGTON, 1952; RUBEL and ROSENTHAL, 1975). Second, if neuronal specificity with respect to the frequency of an adequate stimulus has

anything to do with an organism's ability to differentiate between frequencies (which is by no means certain), ontogenetic behavioral changes (see below) would suggest that tuning curves become steeper with age. Finally, some authors (e.g. KATSUKI, 1961) have suggested that neuronal responses become more specific as one ascends the neuraxis. If one accepts this notion, it is reasonable to believe that the fine adjustments in the local circuitry that determines the parameters of receptive field size may be established consequent to the formation of major projection pathways. Thus, systematic quantitative studies on tuning parameters throughout the developing auditory system are of prime importance for an understanding of the ontogeny of frequency coding in the auditory system as well as for a general understanding of the ontogeny of functional specificity in perceptual systems. Unfortunately, one investigation (AITKIN and MOORE, 1975) has been reported in which the ontogeny of tuning curves was systematically studied. These authors did report the qualitative observation that units in the kitten inferior colliculus became more frequency-specific with age, and presented quantitative data. Average Q values increased with age. However, as the authors point out, Q values normally increase as a function of frequency, and therefore increased responsiveness to high frequencies may be responsible for this change. Had the authors presented quantitative data separately for low frequencies (e.g. 500–2500 Hz), further interpretation might be possible. In any case, the observations of AITKIN and MOORE are important as a preliminary statement. Future researchers should follow their lead, and provide quantitative data on tuning characteristics at brain stem and VIIIth nerve levels, as well as higher levels of the auditory system.

c) The response area of a neuron can be represented by a family of functions showing spike rate as a function of frequency and intensity of a set of stimuli. Ideally, both excitatory and inhibitory zones are shown, by comparison with the spontaneous activity of a cell. Response areas provide a much more complete picture of the stimulus-response contingencies than tuning curves alone, and often yield a very different picture of the complexities of coding than do tuning curves (YOUNG and BROWNELL, 1976). In addition, response areas are dramatically influenced by anesthetics, sleep, etc. Thus, developmental analyses of unit response areas may be of extreme importance; such analyses, in conjunction with morphological studies on the ontogeny of intranuclear and centripetal connections, may yield clues as to the neuronal pathways responsible for the increased coding complexities; and relationships between the behavioral abilities to analyze acoustic information and the ontogeny of neural function may be revealed.

d) Phase locking refers to the extent to which responses of auditory neurons are "locked" to a portion of the stimulating sinusoid, i.e. the degree to which neuronal response intervals tend to be at the period, or some multiple of the period, of the sinusoidal stimulus. There are good reasons to believe that phase locking may be important for low-frequency sound localization, and it may be involved in other acoustic processing capacities. Phase locking is typically found in neurons responsive to low frequencies (<2 kHz) although it has been reported up to frequencies of about 5 kHz. It is most often studied in neurons at relatively low

levels of the neuraxis (VIIIth nerve, cochlear nucleus, olivary nuclei, and inferior colliculus). The only published report on the ontogeny of phase locking is an abstract by JAVEL et al. (1975). In kittens under two weeks of age, they observed phase locking of anteroventral cochlear nucleus cells to frequencies below 300 Hz, but no phase locking to tones above 1000 Hz. It is not known what property of peripheral or central processing is responsible for the limited range of phase locking, but the fact that a cochlear microphonic response to higher frequencies can be recorded suggests sites central to the transduction of mechanical to electrical energy.

e) The ontogeny of binaural response properties of central neurons is another area that has received little attention. One preliminary report (AITKIN and REYNOLDS, 1975) indicates that many inferior colliculus units in very young (5- to 20-day-old) kittens are binaurally responsive. Binaurally excited cells (E/E units) displayed maximum firing to the same frequency applied to either ear (GOLDBERG and BROWN, 1968). Unfortunately, these findings are difficult to interpret; since no controls for interaural communication were performed, ipsilateral stimuli had to be considerably louder (20–40 db) than contralateral tones, and very few units showed opposite responses to the two ears (E/I units) as compared to adults. Future investigations of binaural response properties will be of particular importance. The binaural nature of inputs to brainstem auditory neurons provides a unique advantage for investigations of neurospecificity and the role of experience in the ontogeny of a neuronal structure. Furthermore, quantitative studies on the degree to which binaurally responsive neurons in young animals are “tuned” to similar stimuli will provide additional information on how the fine properties of neuronal coding are established.

f) Response type is the final property by which neuronal responses are often classified. This property refers to the temporal characteristics of responses, as exemplified by post-stimulus-time (PST) histograms. PUJOL and his colleagues (see PUJOL, 1972; CARLIER et al., 1975) have found a common ontogenetic sequence of response types throughout the brain stem auditory system of the kitten. In the VIIIth nerve, cochlear nucleus, and inferior colliculus of very young kittens (less than 7 days old) only “ON” type responses are found; that is, a 500-ms stimulus of adequate frequency and intensity typically evokes one or a few spikes within the first 50 ms and no further activity. At around the seventh day a “rhythmic” response becomes apparent, in which the unit shows alternating period of activity and silence during the stimulus. Initially the silent periods are long (100–300 ms), and they gradually decrease until at 20 days most units respond with an initial burst of discharges followed by sustained activity until the tone is turned off. Although these response types may bear some resemblance to the response types described in the cochlear nucleus by KIANG and his colleagues (e.g. GODFREY et al., 1975), it is probably only a superficial similarity; the ontogenetic sequence is found in the VIIIth nerve, where all units in the adult are of the later-developing “primary” type. It seems reasonable to conclude that these ontogenetic changes are occurring at the periphery. Whether they involve changes in centrally originating efferent pathways (as suggested by CARLIER et al., 1975) is doubtful;

changes in the afferent synapse, such as increased transmitter availability, would be an equally parsimonious interpretation. Future studies in which the periphery is isolated from central influences will be of importance for understanding what acoustic information the developing central nervous system has available. Only then will it be feasible to attempt to understand the ontogeny of auditory information processing in the central nervous system.

5. Responses to Species-Specific Stimuli

The use of pure tone stimuli for auditory neurophysiological investigations has been widely criticized by students of animal behavior, because species-specific acoustic signals usually contain frequency and/or intensity modulations as well as stereotyped temporal modulations between utterances. These critics maintain that neurons selective to the stereotypy ("feature detectors") should be sought, and a number of laboratories are now devoting considerable resources to such investigations. Although some promising results have been reported (e.g. NEWMAN and WOLLBERG, 1973) no convincing examples of cell groups that respond reliably only to the species-specific vocalizations have been found. On the other hand, a number of studies on adult animals have revealed neurons that are selectively responsive to relatively complex parameters such as frequency modulation (e.g. WHITFIELD and EVANS, 1965).

Similar criticisms can obviously be made of the research summarized above on the ontogeny of neuronal responses. While most behavioral research has emphasized that early behavioral responses, especially discriminative responses, are elicited by species-typical complex acoustic stimuli, the neurophysiology of auditory system development has been studied with the aid of pure tones or clicks. One can argue that frequency is a fundamental property of acoustic signals, and therefore merits priority of analysis, but it is also plausible that the auditory system has evolved to give priority to biologically relevant stimuli. In the case of young animals especially, energy and survival considerations would tend to favor the relative disregard for less relevant stimuli. In this respect, it is interesting to note that responses from young organisms can be evoked more readily with tones than clicks, and with long duration tones (500 ms) than short tones (50 ms). Thus, neurophysiological research on young animals, using biologically significant stimulus arrays or synthesized variations thereof, may significantly alter our conceptions of the ontogeny of central auditory processing networks.

6. Behavioral Studies of Sensory Coding

The only way to determine perceptual capacities at any developmental stage is through behavioral studies in which organisms are required to respond differentially to stimuli that differ along some acoustic dimension(s). Only by showing that all stimuli are perceived and that differential responses can be elicited, is it possible to show that a dimension is encoded. The literature on behavioral ontogeny of sensory coding is included in Table 3 and recent reviews of studies in human

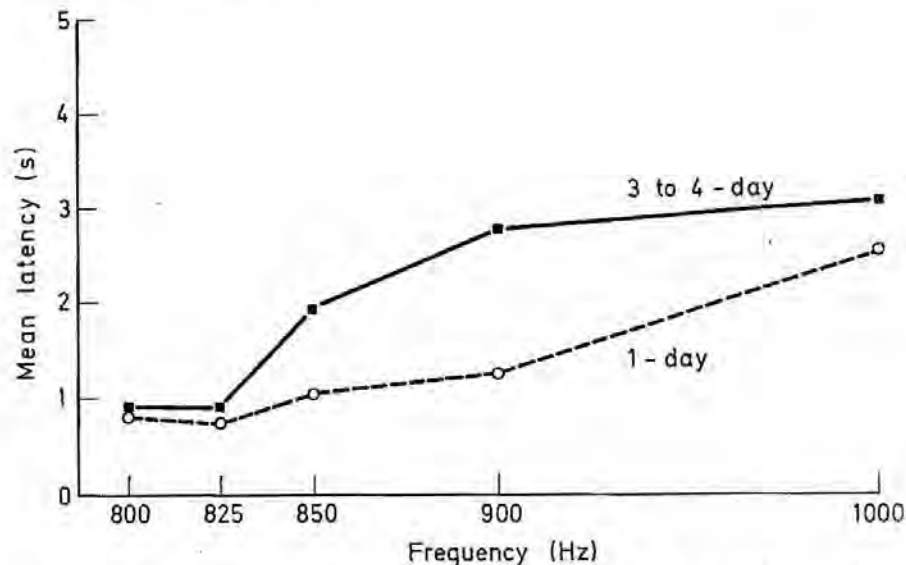


Fig. 8. Generalization gradients as function of stimulus frequency for 1-day-old and 3- to 4-day-old hatching chickens. An orienting response [duration of distress call inhibition-Latency to make distress call following 90 dB (SPL) tone stimulus] was habituated over 12 trials using an 800-Hz stimulus. Separate groups ($N=10$) then tested at 800 Hz (control group) 825, 850, 900, or 1000 Hz. One-day-old chicks show differential orientation only to 1000-Hz stimulus, while 3- to 4-day-olds show differential response to 850-Hz stimulus. (From KERR and RUBEL, 1977)

(EISENBERG, 1976; EIMAS, 1975) and in other species (TEES, 1976) should be consulted for more detail.

Most studies have used complex stimuli in order to determine when language-relevant or species-specific stimuli are differentially encoded. For example, several investigators have shown that phonemic information is encoded by human neonates and there is evidence that categorization may be centered around phonemic boundaries quite early in development. These conclusions are reinforced by the findings of both ear and hemispheric differences in neonatal audition. Equally interesting is the finding that the ability of children to extract relevant acoustic information from background noise continues to improve over the first 10 years.

While there is little information on the development of perceptual encoding by other mammals, studies on avian species with tape-recorded signals have indicated that recognition of species-specific or parental vocalizations emerges after an initial period of undifferentiated responses to acoustic signals. Although these investigations do reveal the time at which biologically relevant discriminations can be made, the complex nature of the stimuli makes it difficult to extract information relevant to understanding of the ontogeny of perceptual encoding along any single acoustic dimension. The use of synthetically altered stimuli, in which each dimension can be individually manipulated, is beginning to alleviate this shortcoming, and promises to reveal important principles (see GOTTLIEB, 1974, 1976b).

Our own studies on the ontogeny of perceptual coding have concentrated on the encoding of a unitary acoustic dimension, frequency, in order to determine if perceptual sharpening occurs with respect to this fundamental property. In two studies (RUBEL and ROSENTHAL, 1975; KERR and RUBEL, 1977) using different responses, it has been shown that the encoding of frequency information becomes

Table 3. Functional Development of the auditory system

Species	Dependent measure	Age ^a (E = Embryonic, P = postnatal)	Stimulus conditions ^{b,c}	Comments	Relevant references
Human	Brainstem evoked potentials	Premature: 34 weeks (E)	Clicks, 10–20/s; 30–55 dB above threshold	No habituation; latency decreases with age; peripheral transmission latency matures earlier (by 6 weeks postnatal) than central transmission, which is mature at about 1 yr postnatal	LEIBERMAN et al. (1973), HECOX and GALAMBOS (1974), BUDA et al. (1975), SALAMY et al. (1975), SCHULMAN-GALAMBOS and GALAMBOS (1975), SALAMY and MCKEAN (1976)
		Premature: 23 weeks (E)	Clicks, 0.25/s; 115 dB	Large latency decreases during weeks 23–33 (E); gradual latency decreases postnatally to 1–2 yr; lateral asymmetry to verbal stimuli present in first weeks postnatal	ELLINGSON (1964), WEITZMAN et al. (1965), WEITZMAN and GRAZIANI (1968), AKIYAMA et al. (1969), ENGEL and YOUNG (1969), MONOD and GURMA (1971), SCIBETTA et al. (1971), GRAZIANI and WEITZMAN, (1972), GRAZIANI et al. (1974), MOLFESE et al. (1975)
		<i>In utero</i> : 32–35 weeks	Tones of 1000 Hz applied to maternal abdomen	Recordings from abdomen above vortex suggest cortical EP with initial latency of 100–150 ms	BARDEN et al. (1968), SAKABE et al. (1969)
	Heart rate	<i>In utero</i> (26–28 weeks)	Tones at 500– 1500 Hz; 100 dB at abdomen; 87–95 dB <i>in utero</i>	Stimulus elicits heart rate acceleration; response to stimuli above 3000 Hz seems to develop later (after 30 weeks); similar results from prematurely delivered neonates; at birth response to white noise more reliable than to tonal stimuli; habituation to tones, dishabituation to frequency change recorded in newborns	SONTAG and WALLACE (1936), BERNARD and SONTAG (1947), BARTOSHUK (1962a, b, 1964), MURPHY and SMYTH (1962), DWERNICKA et al. (1964), JOHANSSON et al. (1964), WEDEBERG (1965), BENCH and MITTLER (1967), SMYTH and BENCH (1967), TANAKA and ARAYAMA (1969), GRIMWADE et al. (1971), JOHANSSON (1972, pers. comm.), GOODLIN and SCHMIDT (1972), TURKEWITZ et al. (1972), BERKSON et al. (1974)

Table 3 (continued)

Species	Dependent measure	Age ^a (E=Embryonic, P=postnatal)	Stimulus conditions ^{b, c}	Comments	Relevant references
	Movement	29-32 weeks. (E); <i>in utero</i> or premature	Clicks, complex noises, or tones at 500-2000 Hz	Complex stimuli probably more effective than simple tones; initially 500 and 1000 Hz elicit more reliable response than 2000 Hz or higher; habituation of movement response, which recovers with stimulus rate change; buzzer 20 dB above back- ground does not influence non- nutritive sucking in 35-40 weeks pre- matures, but inhibition of sucking postnatally	PEIPER (1925), FORBES and FORBES (1927), RAY (1932), SPELT (1938), FLEISCHER (1955), HUTI et al. (1968), LIPSITT (1969), TANAKA and ARAYAMA (1969), KATONA and BERENYI (1974), MILLER (1975)
	Conditioning	32-40 weeks (E); <i>in utero</i>	CS "loud clapper"	<i>In utero</i> , conditioned movement after 100 trials; postnatally, condi- tioned sucking or head turning at 2-4 days; number of trials to criterion and frequency discrimina- tion improve with age	KASATKIN and LEVIKOVA (1935), SPELT (1938), LIPSITT (1969), KRULISOVA (1974)
	Directional eye movements	3-10 min (P)	"Clicker"	Auditory localization apparent at birth; at 2-4 days turn away from loud and toward softer sounds; possibly systematic right-left ear threshold differences. Sound influen- ces visual scanning at 2 days (P)	WERTHEIMER (1961), TURKE- WITZ et al. (1966), MENDELSON and HAITH (1976)
	Selective attention	4-11 yr (P)	Verbal stimuli, white noise background	Ability to extract verbal stimuli from background improves with increasing age	FISHER and RUBENSTEIN (1975), HOWLAND et al. (1975)
Sheep	Cortical evoked potential	90-100 days (E)	Hand clap or click	First response correlated with appearance of spontaneous activity in EEG	BERNHARD et al. (1959), MEYERSON (1967) (see MARTY (1967))

Cat	Endocochlear potential	Birth	Resting	Potential increased from 8.8 mV at birth to 80.4 mV in adult; largest increase during days 9-20 (3.5 mV/day); development of <i>striata vascularis</i> correlated with EP and progresses from basal-to-apical end	FERNANDEZ and HINOJOSA (1974)
	Cochlear microphonic	61 days (E)	Click, tones at 300-400 Hz, above 80 dB	Internal spiral sulcus forming at basal end; tectorial membrane attachment to supporting cells becoming tenuous; tunnels of Corti and Nuel formed in basal turn. High-frequency response matures post-natally. Adult-like by 3 weeks (P)	PUJOL and MARTY (1970), ROMAND et al. (1970), ROMAND (1971), PUJOL and HILDING (1973)
	8th nerve action potential (unit or compound)	Birth	Click, tones at 800-2000 Hz, 100 dB	Latency threshold and fatigability decrease and frequency range broadens; adult-like by 1 month (P). Unit responses initially of "on" type; by 20 days become "sustained"	ROSE et al. (1957), ROMAND (1971), JEWETT and ROMANO (1972), PUJOL and HILDING (1973), CARLIER et al. (1975)
	Cochlear nucleus unit activity	3 days (P)	Tones at 500-2000 Hz, 100 dB	Latency decrease during first month; responses initially "on" type; at 10 days sustained responses predominate; spontaneous activity increases over first month and inhibitory post-stimulus period decreases in length. Phase locking initially to 300 Hz only; units initially broadly tuned	PUJOL et al. (1969), PUJOL (1972), ROMAND and MARTY (1975), JAVEL et al. (1975)
	Cerebellar potentials	5-6 weeks (P)	Click	When reliably recorded, adult-like in latency and waveform	SHOFER et al. (1969)
	Superior olivary nucleus potentials	2-3 days (P)	Tones at 500-2500 Hz, 100 dB	Afferents from cochlear nucleus to superior olive myelinated at birth; 2-3 ms transmission time at age first recorded	ROMAND et al. (1973)

Table 3 (continued)

Species	Dependent measure	Age ^a (E = Embryonic, P = postnatal)	Stimulus conditions ^{b, c}	Comments	Relevant references
	Inferior colliculus potentials	2-3 days (P)	Tones at 500-2500 Hz, 105 dB	Latency initially long; adult-like by 20 days (P). As frequency range broadens and thresholds drop, units become increasingly frequency-specific and Q_{10} 's increase; tonotopic organization apparent at 6-8 days (P). Middle-ear cavitation hypothesized responsible for increased frequency range	PUJOL and GRANIER (1968), PUJOL (1972), AITKIN and MOORE (1975)
	Medial geniculate potentials	2-3 days (P)	Click, tones at 500-2500 Hz; 105 dB	Response initially seen in pars medialis, Latency adult-like by about 25 days (P); unit responses initially "on" type	ROSE et al. (1957), PUJOL et al. (1970), PUJOL (1972)
	Auditory cerebral cortex (AI) potentials	2-3 days (P)	Tones at 500-2500 Hz; 90 dB	Response to clicks matures later than that to tones (6 days). Evoked potential latency, following rate, and amplitude adult-like by 5th week; latency decrease primarily prior to thalamus; potential initially dominated by negative wave with initial positive wave maturation delayed. First unit responses recorded rostral (basal) area of AI; correlated with cochlear maturation in basal turn. Units responsive up to 15 kHz by 8 days; only upper part of apical coil yet to mature. Units show "on" type response initially, followed by more complex coding (at about 3 weeks)	GROSSMAN (1955), ROSE et al. (1957), ELLINGSON and WILCOIT (1960), MARTY (1962), 1967), ELLINGSON (1964), MARTY and SCHERRER (1964), CHALOUPEK et al. (1968), PUJOL and MARTY (1968), VOLOKHOV (1968), SHOBER et al. (1969), KÖNIG et al. (1971, 1972), PUJOL (1972)

Cerebral cortex, association area potentials	2-3 days (P)	Loud click, tones	Evoked potentials in orbital, insular, suprasylvian and periruciate areas at 2-3 days; percent age of units in suprasylvian area responding to click increases from 33% at 8 days to 96% at 1 mo	MAYERS et al. (1971, 1976), PUJOL (1972)
Behavioral responses	6-7 days (P)	Tones and mixed stimuli 108-120 dB	Startle and eye opening response first to low frequency tone or noise band (125-750 Hz); progressive maturation of higher frequency response; directional orienting matures later, approximately 2-4 weeks	TILNEY and CASAMAJOR (1924), FOSS and FLOTTORP (1974), VOLOKHOV (1968)
Dog Cochlear microphonic	4-5 days (P)	"Intense" click	Detachment of tectorial membrane with supporting cells and inner spiral sulcus forming and tunnel of Corti formed in basal turn	PUJOL and HILDING (1973)
8th nerve compound action potential	7-8 days (P)	"Intense" click	Lengthening of outer hair cells and further formation of inner spiral sulcus; adult-like with respect to threshold and frequency spectrum at 15-20 days (P)	PUJOL and HILDING (1973)
Auditory cortex evoked potentials	6-14 days (P)	click	EP initially positive-negative; latency decreases to adult-like by 5-6 weeks; rapid development of EP amplitude and following characteristics (14-30 days) correlated with basal dendritic growth and myelination	ZAHLAVA et al. (1966), CHALOUPKA et al. (1968), FOX (1968a, b)
Behavioral responses	9-15 days (P)	Tones and noise at 500-750 Hz, 108-120 dB	Initial startle response to 500-750 Hz; higher frequencies (2-18 kHz) first elicit responses on days 18-22. Initial directional orientation about 16-24 days (P)	VOLOKHOV (1968), FOSS and FLOTTORP (1974)

Table 3 (continued)

Species	Dependent measure	Age ^a (E = Embryonic, P = postnatal)	Stimulus conditions ^{b, c}	Comments	Relevant references
Mink	Behavioral responses	30 days (P)	Tones and noise at 500-750 Hz, 108-120 dB	Startle responses to higher frequencies mature later	Foss and FLOTTORP (1974)
Rabbit	Cochlear microphonic (CM) and summing potential (SP)	5 days (P)	Tones at 1-7 kHz, 120 dB	Direct stimulation of oval window. CM threshold and frequency response adult-like by 15-20 days. SP polarity reversal at 10-15 days attributed to differentiation of outer hair cells. Onset correlated with formation of inner spiral sulcus, tunnel of Corti, and spaces of Nuel; occur first in basal turn	ÄNGGÅRD (1965)
	Endocochlear potential	5 days (P)	Tones at 1-7 kHz, 120 dB	Develops homogeneously throughout cochlea during 5-15 days	ÄNGGÅRD (1965)
	Brainstem evoked potentials	5 days (P)	Tones at 3 kHz, 125 dB	Response to tones prior to click; latency decreased between days 5-15	ÄNGGÅRD (1965)
	Auditory cortex evoked potentials	4-6 days (P)	Click	Latency and amplitude characteristics develop over first two months; initial responses appear partially from superficial layers, which correlates with synaptology	MARTY (1962), MARTY and SCHERRER (1964), KLYAVINA and OBRASOVA (1968), KÖNIG and MARTY (1974)
	Behavioral responses	6-7 days (P)	Tones and noise at 108-120 dB	Initial startle response to 250-750 Hz; directional orientation first seen on day 12-15; conditioning possible on days 10-11	VOLOKHOV (1968), Foss and FLOTTORP (1974)

Guinea pig	Cochlear microphonic (CM)	48-52 days (P)	Click, tones of 600-2000 Hz, at 100 dB	CM to higher and lower frequencies delayed; amplitude adult-like by birth or a few days after; onset correlated with freeing of tectorial membrane, formation of inner spiral sulcus, and development of fluid spaces, and rapid increases in cochlear enzymatic activity	RAWDON-SMITH et al. (1938), CHONDYNIKI (1968), ROMAND et al. (1971), ROMAND (1971), PUJOL and HILDING (1973)
	8th nerve potential	50-53 days (E)	Click, tones of 1-3 kHz, at 110 dB	Between onset and 2 days (P), latency, waveform and amplitude become adult-like	ROMAND et al. (1971), ROMAND (1971), PUJOL and HILDING (1973)
	Auditory cortex evoked potential (EP)	52-53 days (E)	Click	Latency decreases, amplitude and following rate increase; adult-like soon after birth. At onset negative wave predominates; transient latency increase and decreases anoxia resistance during perinatal period. Responses recorded <i>in utero</i> to external stimulus 40 hrs prenatal	CHALOUPEK et al. (1968), SCIBETTA and ROSEN (1969), ROSEN (1971), SEDLACEK (1974, 1976)
	Behavioral responses	52-60 days (E)	Tones and noise ("loud")	In premature, movement response as early as 52 days (E); Preyer by 61 days (E) to "clang"; at birth (65 days) directional orientation and conditioning observable	AVERY (1928), RAWDON-SMITH et al. (1938), VOLOKHOV (1958), SCIBETTA and ROSEN (1969)
Rat	Endocochlear potential	5 days (P)	—	Low at 8-11 days; rapidly increasing potential during 11-16 days (P); correlates with maturation of <i>stria vascularis</i> , morphology, cochlear microphonic, Na-K-activated ATPase activity, and exploration from the nest site	SCHMIDT and FERNANDEZ (1963), BOSHER and WARREN (1971), KUIJPERS (1974)
	Cochlear microphonic potential	8-9 days (P)	Tones at 200-2000 Hz, 80 dB (re 1 dyne/cm ²)	By 11 days, frequency range up to 10 kHz; 16-20 days (P) adult-like sensitivity and frequency range (to 70 kHz). Opening of meatus (at 12-13 days) lowers thresholds 20-30 dB	CROWLEY and HEPP-RAYMOND (1966)

Table 3 (continued)

Species	Dependent measure	Age ^a (E = Embryonic, P = postnatal)	Stimulus conditions ^{b, c}	Comments	Relevant references
	Brainstem potentials	13 days (P)	Clicks at 70 dB	Latency maturation at relatively younger ages for earlier waves (i.e. most peripheral)	JEWETT and ROMANO (1972)
	Auditory cortex evoked potentials	8-15 days (P)?	Tones and click	Onset varies widely between studies; negativity predominates at early ages; adult-like in latency, waveform, following rate, and amplitude by 28 days	BURES (1953), CHALOUKKA and MYSLIVECEK (1960), CHALOUKKA et al. (1968), VOLOKHOV (1968), KÖNIG and MARTY (1974)
	Behavioral responses	9-12 days (P)	Click, handclap, whistle	Opening of meatus not responsible for functional onset; correlated with initial maturation of responses are apparent innervation of hair cells (day 9), increase in hair cell volume (days 0-10); prolonged increase in ganglion cell volume (days 0-20), development of tunnel of Corti and spaces of Nuel (days 9-15), formation of inner spiral sulcus, etc., (see Wada). Basal-to-apical cochlear maturation. Directed orientation by day 12	SMALL (1899), LANE (1917), WADA (1923), VOLOKHOV (1968), BRACKBILL (1976)
Mouse	Endocochlear potential	Birth	—	Low at birth, adult-like by 14 days (P)	SCHMIDT and FERNANDEZ (1963)

Cochlear microphonic (CM) and 8th nerve action potentials (AP)	8 days (P)	Clicks, tones of 600–2000 Hz at 100 dB	Genus <i>Mus</i> : Meatus opens about day 8 (P); frequency range extends to 8 kHz by day 9 and 40 kHz by day 11; adult-like in 0.6–40 kHz range by 14 days. Cochlear maturation delayed in apical portion. Last morphological change around onset appears to be formation of efferent connections (day 10). AP development parallels CM, but delayed about 24 hrs.	ALFORD and RUBEN (1963), MIKAELIAN and RUBEN (1965), KIKUCHI and HILDING (1965)
Inferior colliculus potentials	15 days (P)	Tone of 15 kHz, at 100 dB	Did not test prior to 15 days or with other frequencies; increasing amplitude of evoked potential coincides with period of susceptibility to priming	LIEFF et al. (1975)
Behavioral responses	11 days (P)	Tones of 1–3 kHz, at 95–110 dB, clicks	<i>Mus</i> : Onset of Preyer reflex coincides with onset of 8th nerve response; response initially to 1–3 kHz at 11–12 days, spreads to 0.5–36 kHz by 14 days, adult-like by 16 days <i>Peromyscus</i> : Startle response to "loud squeak" varies with species (9–23 days P)	ALFORD and RUBEN (1963), MIKAELIAN and RUBEN (1965), POWERS et al. (1966), LAYNE (1968)
Cochlear microphonic (CM) and 8th nerve action potentials (AP)	CM: 12 days (P), AP: 14	Tones of 200–30000 Hz, 80–100 dB	Initial CM responses to almost entire frequency range; thresholds decrease 40–60 dB during 12–23 days (P). Behavioral response, movement, correlated with onset of AP	FINCK et al. (1972)
Opossum (<i>Didelphys virginiana</i>) Endocochlear potential	25–30 days (P)	—	Rapid development between 36 and 75 days; adult-like by 78 days	SCHMIDT and FERNANDEZ (1963)

Table 3 (continued)

Species	Dependent measure	Age ^a (E=Embryonic, P=postnatal)	Stimulus conditions ^{b,c}	Comments	Relevant references
	Cochlear microphonic (CM)	48-50 days (P)	Loud tones at 1-7 kHz	Low-frequency CMs mature before high-frequency responses; peak frequency sensitivity shifts upward; adult-like by 77 days; upper part of basal turn matures earliest; apex matures latest. Middle ear ossification also correlates with CMs. <i>D. marsupialis</i> : onset about 59 days (P)	MCCRADY et al. (1937, 1940), MCCCLAIN (1939), LARSELL et al. (1944)
	Behavioral responses	50 days (P)	Handclap, shrill whistle	Whole body movement initially; 51 days, movement to loud tones of 1-1.5 kHz; pinna reflex and larger frequency range mature during next days. First behavioral response in <i>D. marsupialis</i> at 59 days (P)	LARSELL et al. (1935), MCCRADY et al. (1937)
Chicken	Cochlear microphonic	13 days (E)	Tones of 100-250 Hz; 90-100 dB	Higher frequencies progressively added; threshold frequency increases during development to 2-3 kHz at hatching; amplitude also increases. Possible CM apparent on 10th day (E)	VANZULLI and GARCIA-AUSTT (1963), SAUNDERS et al. (1973)
	Brainstem evoked potentials	11-12 days (E)	Tones of 100-1300 Hz, at 105-120 dB	Response range sensitivity and following rate increase until adult-like at hatching. Thresholds decrease 20-30 dB between day 18 and hatching, possibly due to middle ear cavitation	SAUNDERS et al. (1973, 1974), SAUNDERS (1974)

Midbrain unit responses	1-5 days (P)	Tones of 100-3600 Hz	Unit responses sharply tuned; no inhibition; EEG already well developed	PETERS et al. (1960), ROSOWSKI et al. (1976)
Forebrain evoked potentials	18 days (E)	Clicks	Presumably from field L	SEDLACEK (1974)
Behavioral responses	14 days (E)	Tones of 700, 1000 and 1400 Hz, at 100-115 dB	Reliable change (decrease) in movement on day 14; some authors suggest earlier response. By day 15-16, rhythmic clicks may evoke "conditioned" movement; reliable conditioning to 3 kHz tone by day 17; species-specific maternal call evokes increased activity at 19-20 days. Post-hatching sharpening of perceptual discrimination	GOS (1935), KUO (1938), HUNT (1949), SEDLACEK (1964), GOTTLIEB (1965a), GRIER et al. (1967), SVIDERSKAYA (1967), RUBEL and ROSENTHAL (1975), VINCE et al. (1976), JACKSON and RUBEL (1977), KERR and RUBEL (1977)
Duck Brainstem potentials	19-20 days (E)	Tones of 120-500 Hz; 60-90 dB	Units responsive to progressively higher frequencies and lower thresholds added through hatching; binaural units apparent at youngest ages. Evoked potentials in hatchlings show lowest threshold at 1-2 kHz	KONISHI (1973), SAUNDERS et al. (1974), WOOLF and CAPRANICA (1975)
Behavioral responses	Day 22 (E)	Mallard duck maternal call, 55-66 dB	At age where initial responses observed, ducklings show differential response to species-specific maternal vocalization; response initially inhibitory, becomes excitatory on day 24 (E); at pipping stage, movement-contingent stimulation with maternal call results in more movement during stimulus than randomly presented stimulation	GOTTLIEB (1965b, 1966, 1968a and b, 1971a), IMPEKOVEN (1973)

Table 3 (continued)

Species	Dependent measure	Age ^a (E = Embryonic, P = postnatal)	Stimulus condition ^{b, c}	Comments	Relevant references
Gulls	Behavioral responses	15 days (E)	Species-specific calls, at 80-85 dB	At 15 days (E) increase activity to "crooning," other calls less effective; on first day after hatching, find recognition of individual parent's vocalizations; discrimination increases for 1-3 weeks. Parental recognition at hatching varies with species and type of call	BEER (1970a, 1972), EVANS (1970a, b), IMPEKOVEN (1973)
Guillemots	Behavioral responses	24-36 h before hatching	Species-specific "luring" call	Embryos can discriminate familiar vs. unfamiliar call from same species; at hatching, recognize call of individual parent	TSCHANZ (1968)

^a Age when auditory response is first reliably seen.

^b Stimulus used at age where first auditory response is first seen.

^c Intensity reported at dB *re* 0.0002 dynes/cm² unless otherwise noted.

increasingly finer during the first 3–4 days after hatching in the neonatal chicken. Both experiments used an habituation-generalization paradigm; an orienting response to tone bursts of one frequency was first habituated and then a new set of stimuli, differing by 0, 25, 50, 100 or 200 Hz was presented. Increased orientation during the test trials indicated that the new frequency was being differentially encoded. Results of the study by KERR and RUBEL are shown in Fig. 8. One-day-old and 3- to 4-day-old chicks, while making distress calls, were given 12 trials at approximately 30-second intervals. In each trial, a 90 db, 800-Hz tone was presented for 1.6 s. Initially, the subjects oriented to the tone and ceased emitting distress calls for 5–10 s. With successive trials, the orienting response habituated, and after 12 such trials either the same frequency (800 Hz) or a new stimulus was presented. As seen in Fig. 8, 3- to 4-day-old chicks displayed an orienting response (increased latency to emit distress calls) to an 850-Hz stimulus, while one-day-old chicks did not demonstrate differential responding, except to the 1000 Hz stimulus. These results are identical with those obtained using an eye-opening response (RUBEL and ROSENTHAL, 1975) and indicate that a fundamental acoustical property such as frequency becomes increasingly encoded over the first 3–4 days after hatching. The extent to which similar processes are occurring along other acoustic dimensions and to which this result is generalizable to other species is uncertain. Examination of other ontogenetic changes in perceptual encoding is of importance for understanding neural mechanisms underlying the ontogeny of auditory information processing.

IV. Experiential Influences on Auditory System Development

The influence of experiential events on the ontogeny of neural structure and function within the visual system has been a focus of much recent research. Less attention has been given to this problem by investigators concerned with development of audition. Two major reasons can be identified: i) In comparison with visual features less information is available about the neuronal coding of acoustic features; and ii) It is easier to control gross aspects (light vs. dark) of the visual environment. The relative paucity of literature in this area is unfortunate, since in many ways experimental control of individual parameters of acoustic exposure is easier. Furthermore, in the visual system a large part of the processing is performed at the retinal level, which makes it difficult to analyze the relationships between chronic changes in visual exposure, receptor excitation, and changes at each succeeding neuronal level. In the auditory system, the relationships between hair cell excitation and activity are much clearer, at least at the cochlear nucleus level. As will be seen in Section C. III., the unique segregation of the binaural inputs at brainstem levels affords the opportunity for very detailed cellular analyses (e.g. see BENES et al., 1977).

Table 4 summarizes most of the available literature regarding the influences of early auditory experience on cochlear, central nervous system, and behavior development (see also MISTRETTA and BRADLEY, 1977).

The first item in Table 4 is included to point out that the normal mammalian embryonic environment has potential for a reasonable amount of sound exposure, especially in the low frequency range. Avian species also have the potential for acoustic stimulation during embryogenesis. JACKSON and the present author, using a piezoelectric microphone inserted and sealed into chick eggs, have observed that low-frequency signals (<1500 Hz) are attenuated by 10–20 db, and signals above approximately 1800 Hz are transmitted into the egg with little or no attenuation.

The remainder of Table 4 is devoted to the available examples indicating that early environmental experience effects lasting changes on auditory system development. A thorough coverage of this topic would also include congenital pathologies in humans, known genetic malformations in other animals, and the effects of early acoustic trauma. Human congenital pathologies are beyond the scope of this chapter (see OMEROD, 1960; ALTMANN, 1964; SCHUKNECHT et al., 1965; LINDSAY and MATZ, 1966).

Although the extensive literature on genetically caused malformations of the inner ear has not been included, its possible relevance to the understanding of environmental influences is worth noting. Genetically produced malformations of the inner or middle ear provide naturally occurring manipulations. By causing severe alterations in peripheral input to the central nervous system (CNS), these and other pathological conditions can be used to define a "baseline" for indicating how the CNS responds to gross changes in peripheral input. For this reason, as well as for their clinical relevance, studies defining the etiology, timing, physiological consequences, and behavioral deficits resulting from mutations affecting the inner ear are of great importance. Several "animal models" of congenital deafness have been discovered and a few have been studied extensively (e.g. HUDSON et al., 1962; MIKAELIAN and RUBEN, 1964; MIKAELIAN et al., 1965, 1974; DEOL, 1967, 1968, 1970; BROWN and RUBEN, 1969; RUBEN, 1973; SUGA and HATTLER, 1970; MAIR, 1973). The recent introduction of *in vitro* methods for investigation of the etiology of genetically caused inner ear malformations (VAN DE WATER and RUBEN, 1974) promises significant advances in this field. Relatively little work has been directed toward elucidating the effects of degenerative mutations of the inner or middle ear on central nervous system development. The most significant contribution (WEST and HARRISON, 1973) describes severe reductions in cell size in some areas of the cochlear nucleus and superior olivary complex, with little or no atrophy in other areas of these brainstem auditory nuclei in two adult deaf white cats. Although similar but less severe effects were found in one young mutant cat, the subject population was too small to yield definitive conclusions. Future investigations in this area should use mutant mice or some other preparation in which sufficient subject populations are available to permit thorough developmental analyses. A systematic effort along these lines could yield important principles for understanding the role of peripheral input on central nervous system ontogenesis. One caution bears consideration. While mutant preparations may provide a powerful tool, the primary etiology of the syndrome is seldom, if ever, clear. That is, when the primary effect of the mutation is on the developing neural tube (e.g. VAN DE WATER and RUBEN, 1974), the interpretation of central nervous system changes becomes more difficult; any given difference between neurons in normal and mutant animals may result from either direct effects of the mutation, indirect (transneuronal) influences, or a combination of both.

The effects of acoustic trauma (and high-intensity noise exposure) on the developing cochlea, auditory pathways of the brain, and auditory perception, has been thoroughly reviewed by SAUNDERS and BOCK (1977). Thus Table 4 includes only a few of the available references. Two points merit added emphasis. First, it appears that in young as well as older animals, high-intensity noise exposure induces permanent structural changes in the inner ear; in fact, the available data strongly suggest that the cochlea of young animals may be hypersusceptible to acoustic trauma. Second, SAUNDERS and his colleagues have built up a convincing case for the idea that similar events are occurring with the induction of seizure susceptibility through priming in normally seizure-resistant mice. Their data show that primed mice have increased evoked potential thresholds, coupled with hyperresponsivity to high intensity stimuli. Although they have likened the latter effect to discuss supersensitivity, direct evidence of changes in central nervous system pathways is not available. In any case, the conclusion that priming serves to "deprive" the central nervous system of normal sensory activation indicates that this preparation may be useful for understanding the morphological and physiological effects of auditory deprivation. However, a thorough analysis of the effects of priming on the developing cochlea itself is a critical step; then it will be possible to ascertain how priming influences the activity impinging on the central nervous system (CNS) and thereby alters normal neuronal input.

Systematic attempts to understand how the ontogeny of neurons or neuronal networks is influenced by auditory experience are lacking. The few studies noted in Table 4 that have found changes in CNS anatomy or physiology have failed to distinguish between alterations of normal ontogeny and degenerative effects (cf. SOLOMON and LESSAC, 1968; GOTTLIEB, 1976a). Following examples provided by studies on the mammalian visual system, the principal paradigm has been to subject one group of animals to acoustic deprivation or alteration of the sound patterns heard, and then make comparisons between these "experimental" subjects and normal animals as adults. Typically, one neuronal locus is arbitrarily examined with respect to cellular responses or evoked potentials. While such studies may demonstrate an *influence* of acoustic experience on neural responses, they provide little more. Failure to examine the cochlea or output thereof means that the site of the "effect" is unclear; failure to examine the normal ontogeny of the process under investigation, means that the developmental nature of the "effect" cannot be interpreted; failure to sample systematically within the arbitrarily chosen neuronal population means that the specificity of the "effect" is obscured; and failure to determine how the manipulation itself influences neuronal activity within the auditory system, the mechanism(s) responsible for the effect remain(s) undeterminable. Although these criticisms may appear unduly harsh, it is the opinion of this author that attempts to ascertain the influence of early experience on sensory system development should envision more than demonstrating "an effect"; systematic control of the acoustic experience and careful analysis of structural and functional changes at successive levels of the auditory system could lead to more complete understanding of general principles.

Behavioral analyses of experiential influences on auditory perception have been more systematic, especially those using avian species. Essentially four methods have been used: i) Auditory deprivation; ii) Alterations of the normal acoustic environment by application of artificial stimuli; iii) Artificial application

of normally occurring stimuli or some variation thereof; and iv) Inferential analysis drawn on correlations of early acoustic experience and later behavioral responses.

Broad-band auditory deprivation appears to retard the development of several auditory functions. WOLF's (1943) early studies indicated that when rats are reared in relative sound isolation, learning to use an acoustic signal as a cue for finding food is retarded. TEES (1967a, b) found that perceptual discriminations of stimulus duration and pattern are impaired. Since neither investigator examined normal ontogeny of auditory perception, the developmental nature of these deficits cannot be assessed. Studies on ducklings and chicks, on the other hand, have addressed development. GOTTLIEB's investigations of duckling embryos and hatchlings (Section C.I) have shown that the development of differential responsiveness to species-typical call characteristics, including repetition rate, dominant frequency, and frequency subunits, is delayed when the organisms are deprived of hearing their own and their siblings' vocalizations. Our own investigations of the influence of auditory experience have concerned the ontogeny of differential responsiveness to stimulus changes that vary along the frequency dimension. After confirming that 3-4-day-old neonatal chickens make finer frequency distinctions than 1-day-old hatchlings (Fig. 8) KERR and RUBEL (1977) used plastic ear plugs to attenuate auditory input over this period. The ear plugs were evaluated by brainstem evoked potential frequency threshold functions, and found to attenuate acoustic input 38-42 dB across the entire audible range. Figure 9 shows the results of generalization testing on deprived animals 45 min after the ear plugs were removed, compared to results from normal 3- to 4-day-old chicks, and chicks that went through the deprivation procedures except for insertion of the ear plugs (shams). The results clearly show that deprived subjects have flatter generalization functions than either normal or sham subjects, and were comparable to 1-day-olds in Fig. 8. It is of importance that the deprived animals do not differ from the other groups at 800 Hz or 1000 Hz, indicating that the results are not due to differences between the groups in either "general arousal" or sensitivity to acoustic stimuli (i.e. increased thresholds), but are specific to categorization of sounds along the frequency dimension. Taken together, Figs. 8 and 9 clearly indicate that deprivation has retarded the normal perceptual sharpening that takes place during the first 3-4 days after hatching in the chicken. Whether this retardation of perceptual discrimination will be corrected during longer periods of deprivation or with exposure to a normal acoustic environment, and the extent to which the perceptual sharpening is dependent on the specific frequencies available in the organism's environment are problems currently being investigated.

Experiments in which an artificial auditory stimulus is applied during some period of embryogenesis, and later behavior is examined (see Table 4, Item 5) are of interest for at least two reasons. First, as noted by GOTTLIEB (1968a), it should not necessarily be presumed that the perception of a sensory stimulus will lead to a measurable motor response. That is, the formation of sensory-driven reflexes, which require a connection between the receptor-activated neural pathways and effector networks, may evolve under different selection pressures than the receptor systems themselves. For example, if externally or internally generated stimuli are important for the organization of the receptor and neural information processing

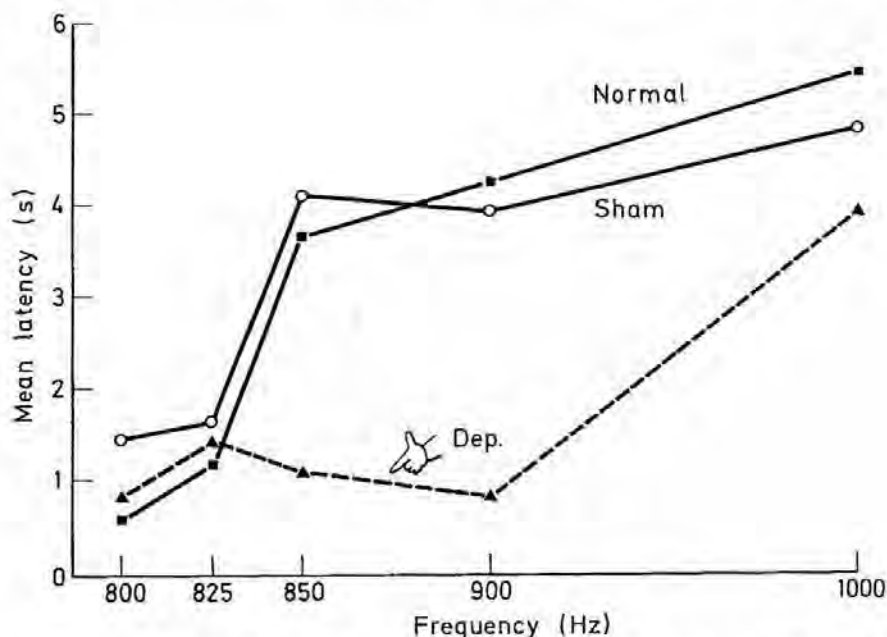


Fig. 9. Same paradigm as Fig. 8. Three groups of 3- to 4-day-old chickens (50/group) were used. Deprived (Dep) subjects had been deprived of 40–45 db acoustic stimulation from embryonic day 18.5 until approximately 1 hr before testing. “Sham” subjects were treated like deprived group except for actual acoustic deprivation. “Normal” subjects were untreated controls. All subjects were habituated (12 trials) to 800-Hz (90 dB, SPL) stimulus and then tested at one of indicated frequencies (each data point represents mean of 10 subjects): 800 Hz (control group for each age), 825 Hz, 850 Hz, 900 Hz, 1000 Hz. “Latency” indicates time to resume distress calling following stimulus, time subject orients to the stimulus. Normal and “sham” subjects show differential orientation at 850 Hz, while subjects deprived of normal acoustic experience do not show differential orientation until 1000 Hz—200 Hz from training stimulus. (From KERR and RUBEL, 1977)

networks, such stimuli may not elicit any observable reflexive response. Thus, one method by which the onset of sensory function can be determined is through brief exposure to a stimulus at one point in development and later assessment of its influence on behavior development. The second and more usual rationale for these experiments is to ascertain how embryonic stimulation may influence later behavioral responses, such as conditioning or following preferences. Of at least equal importance are possible effects of sensory experience on the rate of behavior development, e.g. time at which hatching occurs (see VINCE, 1973).

Experimental manipulations of an organism’s normal acoustic environment have been systematically attempted only for avian species⁴. Most such studies are concerned with how specific aspects of an organism’s auditory experience come to control species-specific or individual-specific perceptual preference behaviors. By systematically varying the parameters of acoustic stimuli impinging on the avian embryo, GOTTLIEB has shown that preference behavior can be markedly influenced. Such manipulations may also influence the rate of perceptual development (GOTTLIEB, 1971a) and the rate of behavioral and physiological maturation processes in general (VINCE, 1973). Thus, it is critical that future investigations are

⁴ In addition to the studies listed in Table 4, the extensive literatures on the effects of auditory experience on the ontogeny of bird song and human language are relevant, but not considered, as these subjects concern primarily “production” rather than “reception”.

Table 4. Experiential influences on auditory system development

Treatment/dependent variable	Species	Comments	Relevant references
1. Sound in prenatal environment Human and goat	Human, goat	Intrauterine ambient noise in low frequency range (20–200 Hz) as high as 90 dB (SPL); attenuation of environmental sounds increases from 20 dB @ 50 Hz to 50 dB @ 2000 Hz	WALKER et al. (1971), BENCH (1968), BENCH et al. (1970)
2. High-intensity sound exposure (cf. SAUNDERS and BOCK (1977) for review) Human hearing loss		Available data suggests increased susceptibility to loss of high frequency sensitivity with repeated childhood exposure	WEBER et al. (1967), MILLS (1975), (Review), SAUNDERS and BOCK (Review)
Noise adaptability	Human	Prenatal environment may influence adaptability to postnatal noise exposure	ANDO and HATTORI (1970)
Cochlear changes	Cat, guinea pig, mouse	Immature cochlea shows increased susceptibility to temporary and permanent threshold shifts as well as permanent structural damage	LURIE (1940), PRICE (1972), FALK et al. (1974), SAUNDERS and HIRSCH (1976)
CNS changes	Mouse	“Primed” mice of normally seizure-resistant strains show increase in evoked potential thresholds coupled with increased amplitude of evoked potential at high intensity (loudness recruitment), lowered threshold for Preyer reflex and seizure susceptibility	HENRY (1972), WILLOTT and HENRY (1974), HENRY and HAYTHORN (1975), SAUNDERS and BOCK (1977)
3. Neonatal asphyxiation	Human, kitten	Perinatal asphyxiation can decrease cell number and nuclear volume in cochlear nuclei; changes appear permanent	HALL (1964)
4. Auditory deprivation CNS anatomical changes	Mice	Binaural deprivation during days 3–45 resulted in decreased cell size and neuron density in some brainstem nuclei, and increased packing density in inferior colliculus	WEBSTER and WEBSTER (1976)

CNS physiological changes	Rat	<p>Monaural deprivation during first month resulted in loss of ipsilateral inhibitory influences in inferior colliculus. Deprivation for 8 months resulted in evoked potential threshold increase of 30-60 dB which disappeared following 3 weeks' exposure to normal environment</p>	<p>BATKIN et al. (1970), SILVERMAN et al. (1975)</p>
Behavioral changes—mammals	Rat	<p>Early auditory deprivation resulted in deficits in learned response to acoustic signal when compared with visually deprived subjects after 10 days of normal environment. Immediate deficits after deprivation for first 60 days in duration and pattern discrimination learning but no deficits in simple frequency or intensity discrimination learning</p>	<p>WOLF (1943), GAURON and BECKER (1959), TEES (1967a and b, 1976)</p>
Behavioral changes—birds	Ducks, Chicks	<p>In duckling deprivation retards development of normal embryonic changes in response to species-typical calls and disrupts posthatching perceptual preferences for normal species-typical calls by interfering with ontogeny and maintenance of high-frequency selectivity. Normal sharpening of frequency generalization gradient fails to occur during deprivation</p>	<p>GOTTLIEB (1968a, 1971a, 1976b), KERR and RUBEL (1977)</p>
5. Altered acoustic environment CNS changes	Rats, Hamsters	<p>Selective exposure of rats to increasing or-decreasing frequency modulation during first 4 months tends to depress inferior colliculus unit responses to white noise following <i>unfamiliar</i> modulation; little or no effect on number of units responding to either FM stimulus. Global "enrichment" by continuous exposure to radio does not influence latencies. In hamsters continuous exposure to 85 dB white noise during first 3 months increases cortical evoked potential threshold; possible cochlear damage also</p>	<p>CLOPTON and WINFIELD (1974, 1976), MAILLOUX et al. (1974), PUJOL et al. (1975)</p>
Lack of CNS change	Cat	<p>No change in inferior colliculus unit responses following increase in daily exposure to 1000 Hz tone</p>	<p>MOORE and AITKIN (1975)</p>

Table 4 (continued)

Treatment/dependent variable	Species	Comments	Relevant references
Behavioral changes	Chicks, quail	Exposure to intermittent tone during embryonic days 13-18 increases posthatching "attractiveness" of the familiar frequency; and conditioning to bell during late embryogenesis may influence postnatal response to bell. Brief (2 h) stimulation with broad-band noise may accelerate hatching in quail	HUNT (1949), GRIER et al. (1967), RAJECKI (1974), WOOLF et al. (1976)
6. Artificial variations of normal acoustic environment Behavioral influences	Guillemots, gulls, ducklings	Perinatal exposure to parental, siblings' and self-produced calls influences postnatal behavioral response specificity by: i) determining individual characteristics of parental call recognition (guillemots and gulls); or ii) affecting rate of development and maintenance of preference for species-typical characteristics	TSCHANZ (1964, 1968), GOTTLIEB (1966, 1971a, 1976), IMPEKOVEN (1969), IMPEKOVEN and GOLD (1973)
7. Inferential Analysis of Naturally Occurring Prenatal and Perinatal Stimuli Postnatal behavior	Gulls	Approach responses of chick initially unselective with respect to parental or unfamiliar call but specific to call-type; over first 2-3 weeks becomes specific to parental vocalizations but nonselective regarding call-type	BEER (1970a, b, 1972), EVANS (1970a, b)
	Humans	Heartbeat sound played to newborn infants resulted in increased weight gain and decreased crying; heartbeat played to 3-year-olds resulted in decrease in latency to fall asleep	SALK (1962)
8. Crossmodal effects Cortical development	Mice, rats	Neonatal visual deprivation, eye enucleation or vibrissa removal resulted in altered growth of cells and increased dendritic spines in auditory cortex	GYLLENSTEN et al. (1966), RYUGO et al. (1974)

designed in a way that will allow dissociation of general metabolic from specific perceptual effects.

The last method that has been used to examine the role of auditory experience in perceptual ontogeny attempts to correlate the normal auditory experience of an organism with later perceptual behavior. The research of BEER and EVANS on gulls has convincingly shown that experience of the chick allows it to recognize individual nuances of the parental voice, and to generalize this throughout the range of parental vocalizations. A conceptually similar approach was used in experiments with human neonates and toddlers by SALK (1962). Although the latter publication received much attention in the popular press, it has been largely and unjustly ignored in the scientific literature. The theoretical and practical importance warrants replication and extension of SALK's findings.

Finally, intermodal influences on the ontogeny of the auditory system should be considered. Two investigations suggest hypertrophy of the auditory cortex following alterations in visual and somesthetic stimulation (Table 4, Item 8). While a great deal more research is needed in this area, these studies imply that "increased reliance" upon the auditory system may affect the development of neuronal elements. Thus, an integrated series of behavioral and neurological investigations of the effects of crossmodal manipulations may yield additional understanding of how psychological constructs such as "attention" are transformed into meaningful neuronal attributes contributing to the regulation of behavior.

C. Developmental Neurobiology and Auditory System Ontogeny

This section gives brief descriptions of three research programs in which the vertebrate auditory system is being investigated in order to solve general problems of developmental neurobiology. The purpose is to demonstrate that some of the unique characteristics of the vertebrate auditory system make it especially applicable for illuminating general principles of nervous system and behavior development. In addition to the research program currently under way in the present author's laboratory, GOTTLIEB's investigation of the ontogeny of species-specific perceptual behavior in embryonic and neonatal ducklings, and MOREST's examinations of neuronal migration, synaptic terminal growth, and dendritic elaboration are described. Of the many excellent research programs involving the elaboration of auditory processes, these two have been selected principally because of their contributions toward an understanding of general problems of developmental neurobiology, their systematic nature, and the present author's own familiarity with them. The summaries below are not intended to provide a thorough review of the authors' work, but rather to provide an overview, and to exemplify how study of the developing auditory system may increase understanding of general principles of nervous system and behavior development.

I. The Ontogeny of Species-Specific Perceptual Behavior

While other investigators interested in perceptual development, especially preference behavior, were stressing the importance of imprinting for determining the stimulus characteristics guiding responsiveness to environmental stimuli, GOTTLIEB (1965a) discovered that when given a choice between a parental call of their own species and that of another species, naive ducklings and chicks overwhelmingly approach and follow the species-typical stimulus. Furthermore, even after extensive exposure or active "imprinting training" with the atypical stimuli, a clear preference for the mallard maternal call over that of the chicken or wood duck is shown by Peking (domesticated mallard) ducklings. In addition to calling for a re-evaluation of the interpretations commonly associated with imprinting, this series of studies posed the important question: During the normal course of ontogeny, what factors are responsible for the development of species-typical ("innate") behaviors? GOTTLIEB (1976b) and others have reviewed the various theoretical arguments around this question. Basically it comes down to the following distinction. Do the neural networks responsible for species-typical behaviors arise without relevance to an organism's sensory environment or behavior, or is the stereotype of the final phenotype partially due to commonalities of the developing organisms' interactions with their environment? GOTTLIEB's original discovery of a marked preference for the species-typical maternal call among naive chicks and ducks was taken by some as an indication that perceptual preference behavior developed without regard to an organism's sensory environment. However, strongly influenced by the teachings of KUO (see KUO, 1967), GOTTLIEB has utilized this preparation to show that an organism's sensory environment, an important part of which is self-generated, plays an important role in the development of species-specific perceptual distinctions.

The specific details of these studies can be found in the original reports and have already been summarized (see GOTTLIEB, 1971a, 1976b). Briefly, in one series of investigations, the embryonic development of the ducklings' ability to differentially respond to the species-typical maternal call was evaluated. It was found that 4-5 days prior to hatching (days 22 and 23) the mallard call causes a reliable decrease in bill movement, while on day 24, when the animals normally enter the air space and pulmonary respiration begins, the mallard call begins to elicit an increase in bill movements and vocalizations while other calls do not elicit reliable changes in these activities. Following collection of these baseline data on normal, communally incubated embryos, GOTTLIEB demonstrated that by incubating eggs in sound-isolated compartments or exposing eggs to increased auditory stimulation (sibling calls played over a loudspeaker), the time at which the bill-clapping response to the mallard maternal call shifted from inhibitory to excitatory could be retarded or accelerated, respectively. While it is not possible to ascertain from these results whether the acoustic manipulations caused a generalized change in developmental rate (e.g. VINCE, 1973) or specifically influenced maturation of the auditory system, these findings do suggest that the kind of acoustic stimulation to which embryos are normally exposed influences the development of differential responding to species-typical vocalizations. The fact that 22-day-old embryos

respond selectively to the mallard maternal call indicates that the ontogeny of the inhibitory response is independent of auditory experience.

In the second series of studies, GOTTLIEB directly tested the idea that an organism's own behavior can provide stimulation that influences the development of perceptual preference behavior. The development of a procedure for devocalizing duckling embryos (GOTTLIEB and VANDENBERG, 1968) allowed complete control over the acoustic environment. When devocalized, isolated ducklings were given a choice between the mallard maternal call and that of the wood duck or chicken, they were found to be deficient. Normal ducklings 24 hrs after hatching show an overwhelmingly preferential approach toward the mallard call; ducklings deprived of hearing their own and siblings' vocalizations during the perihatching period did not show a reliable preference between mallard and wood duck calls until later than normal hatchlings, and did not preferentially choose the mallard over the chicken call at 48 or 60 hrs after hatching (GOTTLIEB, 1971a). Upon further analysis of these deficits (see GOTTLIEB, 1976b, for summary), it has been found that both the repetition rate of notes in the maternal call and frequency parameters are bases on which normal ducklings choose the species-typical call. When deprived of hearing their own vocalizations or those of their siblings, deficiencies in the development and the maintenance of the discriminative behavior result, and when provided with supplementary stimulation that contains the appropriate parameters, the preferential responding is regained.

In summary, GOTTLIEB has capitalized on the auditory perceptual behavior of avian embryos and hatchlings to demonstrate that the neural substrate responsible for the ontogeny of species-typical or "innate" behaviors may be powerfully influenced by normally occurring environmental events, some of which are provided by the developing organism itself. GOTTLIEB himself has put it more fully in the following passage from his 1971 monograph:

Because of the demonstrated contribution of normally occurring stimulation in regulating the embryo's and hatchling's usual responses to the maternal call of their species, it can be said that the epigenesis of species-specific perception is a probabilistic phenomenon, and does not represent merely an unfolding of a fixed or predetermined organic substrate independent of normally occurring sensory stimulation. According to the present results, natural selection, insofar as it has played a role in the evolution and maintenance of species-specific perception, would seem to have involved a selection for the entire developmental manifold, including both the organic and normally occurring stimulative features of ontogeny (pp. 148—149).

II. Post-Mitotic Migration and Differentiation of Neurons in the Central Nervous System

In what is deservedly becoming a classic series of reports (MOREST 1968, 1969a, b, 1970a, b), MOREST has made several important contributions to our understanding of the processes involved in neuronal differentiation. The problem addressed by MOREST can be stated as follows. Given that neurons are assembled in definitive locations, and that at a given location many of the architectural characteristics of

both presynaptic and postsynaptic processes are highly stereotyped, how are these factors regulated? More specifically, what causes the soma of a neuron to migrate to a specific location and by what route does it get there? What factors lead to the stereotyped form of terminal arborizations in a given location, especially when collaterals to another location have a completely different form? And by what means do particular dendrites of a neuron acquire their highly stereotyped form, when other dendrites of the same neuron have very different architecture? While MOREST's studies do not, by any means, answer these complex questions, they do provide important insights toward eventual clarification.

In contrast with the experimental investigations described above, MOREST's studies used tissue from normal animals. A second important difference is that while GOTTLIEB's research program has a single overriding theoretical premise, the present studies are descriptive in nature, attempting to define the normal sequence of events occurring in the development of a neuron and then inferring possible causal relationships. Finally, GOTTLIEB's empirical work is restricted to the ontogeny of perceptual behavior in chicks and ducklings, and the generality of his findings remains to be determined; whereas MOREST made his initial observations on auditory centers of the brainstem, principally the medial trapezoid nucleus (MOREST, 1968, 1969a), but has made the additional important step of assessing their generality in other parts of the brain (MOREST 1969b, 1970a, b).

MOREST has primarily used a modification of the rapid Golgi method (MOREST and MOREST, 1966) and supplemented this with tissue impregnated by Golgi-Cox and Golgi-Kopsch methods. The ontogeny of the principal neurons of the medial nucleus of the trapezoid body formed the basis of the original observations. This nucleus, which receives a principal input in the form of large calyces of Held from the contralateral ventral cochlear nucleus, was chosen because of several unique characteristics. First, the principal cells are large neurons, characteristic in shape, that can be recognized throughout most of mammalian embryogenesis. Second, their dendritic arborizations are sufficiently distinctive that throughout development they can be differentiated from dendrites of the stellate and elongate cells of the same nucleus. Third, each principal neuron perikaryon receives synaptic input from one and only one axonal calyx of Held. Finally, the calyces of Held are among the largest synaptic endings in the mammalian brain; they are architecturally homogeneous, and they are only seen on the cell bodies of the principal neurons; because of these characteristics they can be unambiguously recognized throughout their development. These characteristics, therefore, yield a preparation uniquely suited to analyses of the normal ontogeny of post-mitotic neuronal development, especially with respect to temporal characteristics of changes in presynaptic and postsynaptic elements occurring during the period of synaptogenesis.

Three aspects of neuronal differentiation were clarified in MOREST's papers: i) The final stages of neuronal migration; ii) The elaboration of presynaptic elements; and iii) The elaboration of dendrites. Most previous descriptions of the migratory action of neurons were made from Nissl-stained material and pictured undifferentiated, round cells from the mantle layer moving by ameboid action through adjacent tissue to their final resting place. After arriving at the final destination, axons and dendrites were presumed to extend from the soma, and

concurrently or soon thereafter afferent axons formed synapses on the cell body and dendritic processes. By following the presynaptic and postsynaptic elements of the principal neurons of the medial trapezoid nucleus from closely timed litters of cats, rabbits, and opossums, MOREST proposed quite a different view. When first recognized, the neogenic neurons lie near the outer limiting membrane, to which they are attached by a process ending on the membrane. Another process extends toward the lumen. Both processes are characterized by large growth cones and numerous filopodia. As the afferent axons grow into the area that will later become the medial trapezoid nucleus, they initially contact the internally extending primitive process. The axonal extension of the principal neuron apparently arises from this internal protoplasmic process at a site within what will become the nuclear boundary. The nucleus of the neuron moves through this internal primitive process, to a position adjacent to the origin of its axon and where the presynaptic endings are differentiating.

The incipient calyces of Held grow in the trapezoid body through the ipsilateral nucleus, apparently without forming connections with the principal neurons or their processes. Continuing in the decussation of the trapezoid body, they enter the position of the medial nucleus as large growth cones with numerous filopodia radiating through the tissue. When they approach and contact a principal neuron or its internal process, many thin sinuous branches entwine the postsynaptic elements. Gradually, as the neuronal nucleus moves into the vicinity of the afferent ending, the branches either coalesce or are replaced by the broad branches forming definitive calyciform endings. After forming its definitive calyx on one principal neuron, the afferent fiber issues collateral growth cones, which eventually ramify extensively in the surrounding areas of the nucleus.

Dendritic differentiation appears to follow a similar course. Dendrites arise from the neogenic principal neurons as growth cones with abundant filopodia extending from the dendritic ramifications and cell body alike. Gradually, the dendrites establish their stereotyped branching pattern and spine configuration while losing the transitory filopodia. Concurrently with the elaboration of dendritic stereotypy, afferent axons form their characteristic presynaptic configuration. That is, "the development of the dendritic branches accompanies the elaboration of the particular type of axonal plexus that will become synaptically related" (MOREST, 1969a, p. 271).

These descriptions of the events surrounding synaptogenesis and dendritic elaboration are normative. They provide a catalog of several important morphogenetic events, and a timetable of their occurrence. By close examination of simultaneously and successively occurring processes in functionally related neuronal elements, MOREST was also able to make a number of provocative suggestions regarding the importance of temporal contiguities and mutual interactions of incipient presynaptic and postsynaptic processes for sculpting the final functional elements. Although most of the hypotheses put forth regarding the inductive roles of presynaptic and postsynaptic elements remain to be adequately tested, the heuristic value of these contributions for understanding the elaboration of neuronal networks is evident. Furthermore, thorough descriptions of this kind are necessary before definitive experiments can be designed or their results interpreted.

III. Peripheral Influences on the Ontogeny of Neural Structure and Function

The research program presently under way in the present author's own laboratory is in many respects an attempt to integrate the approaches and findings of GOTTLIEB and MOREST. Simply stated, the overall objective is to understand the ways in which the development of neural structure and function are influenced by stimuli impinging upon an organism from its environment. While this is not a unique problem, most previous approaches have utilized the mammalian or amphibian visual system (see Chapter 7). Although these preparations have yielded a number of interesting discoveries, general principles by which experiential events affect the ontogeny of neuronal networks have not been forthcoming. The characteristics of structural and functional organization found in the avian brainstem auditory pathways offer a system uniquely suited to investigations relating neural ontogeny to afferent input.

Two considerations have guided our work on this preparation. First, the assumption is made that an organism's sensory experience influences neural ontogeny through chronic changes in the amount or pattern of afferent activity impinging on the nervous system. Thus, to understand the principles of experiential influences it is necessary to determine the effects of known changes in the quality or quantity of afferent input on the functional and structural ontogeny of neural networks. Viewed in this way, "experiential influences" are considered as one type of tissue interaction that may play a role in the ontogeny of neural elements and the relative influences of both drastic and subtle changes in afferent input at each stage of development are of importance. While total elimination of afferents to a neuron almost certainly interrupts more cellular processes than subtle changes in the pattern of synaptic activation, at least a portion of the syndrome produced by denervation is due to the elimination of synaptic activity. Thus, the examination of developmental changes produced by total removal of a class of afferents should yield a catalog of events, each of which can be systematically evaluated upon progressively more subtle manipulation of the afferent supply.

The second consideration refers to the necessity of using a developmental approach to the processes under examination. That is, for a full appreciation of the principles by which afferent input can influence the development of structure within a neural network, it is necessary to understand the normal sequence and timing of developmental events. Only then is it possible to ascertain the developmental nature of changes induced by perturbations of the neuronal environment (SOLOMON and LESSAC, 1968; GOTTLIEB, 1976a). Furthermore, as exemplified by the work of MOREST, a thorough normative analysis can often provide valuable insights into the possible tissue interactions responsible for the ontogeny of normal neural structure and function.

These and other considerations led the present author to select the avian brainstem auditory pathways for investigation. More specifically, *nucleus magnocellularis* and *nucleus laminaris*, which are comprised of 2nd- and 3rd-order auditory neurons respectively, appeared to be uniquely suited to investigations of

the role of afferents in neuronal development and maintenance. Furthermore, behavioral studies on the ontogeny of auditory information processing provided an interesting behavioral parallel in which the role of acoustic experience could be investigated. Our initial investigations (RUBEL and PARKS, 1975; PARKS and RUBEL, 1975) were primarily intended to provide detailed structural and functional information on the organization of this neuronal system, in order to determine its applicability to this line of investigation. The normal morphological ontogeny of *n. magnocellularis* and *n. laminaris* at the light microscope level was then described (RUBEL et al., 1976), and these observations are currently being extended by neurophysiological and electron microscopic analyses of normal development. Finally, the present author's group has begun to describe how modifications of afferent input can alter the development and maintenance of the normal neuronal elements in this system (PARKS and ROBERTSON, 1976; JACKSON and RUBEL, 1976; BENES et al., 1977; PARKS and RUBEL, 1977). The following account briefly describes the results of these investigations. The emphasis will not be a close examination of the results obtained in these studies, but to show how the unique characteristics of this particular neuronal system make it ideally suited to a thorough analysis of the various roles that afferent information may play in the ontogeny of neural structure and function.

The primary auditory pathways to the medulla of the chicken embryo and hatchling are schematically shown in Fig. 10. Axons of the first-order neurons, situated in the cochlear ganglion, enter the dorsolateral quadrant of the medulla and bifurcate into a lateral and a medial bundle. The lateral branches terminate in a cochleotopic manner in nucleus angularis (NA), which is a triangular nucleus composed of mixed cell types lying in the dorsolateral angle of the medulla. The medial branches of the VIIIth nerve course along the floor of the fourth ventricle (IV) to terminate in *n. magnocellularis* (NM). *N. magnocellularis* is a well-defined cluster of large round or ovoid cell bodies, which are either devoid of dendrites or have short bushy rudimentary dendrites. The cells are organized in a columnar manner (dorsal-ventral or dorsolateral-ventromedial) with VIIIth nerve afferents coursing between the columns and terminating principally on the cell bodies as large endbulbs. As also shown in Fig. 10 *n. laminaris* (NL) in chickens is composed of a discrete monolayer of cell bodies with bipolar dendritic orientations. Cells of *n. laminaris* receive binaural, spatially segregated innervation from the magnocellular nuclei; axons from NM pass in the uncrossed dorsal cochlear tract to innervate the dorsal dendrites and cell bodies of the ipsilateral *n. laminaris*, and decussate in the crossed dorsal cochlear tract to innervate the ventral dendrites and the cell bodies of the contralateral laminar nucleus. This relatively simple structural organization, the accessibility of avian embryos for neurophysiological studies or peripheral manipulations, and the possibilities for precise control over the acoustic environments of embryos and hatchlings, warranted further investigation of the functional organization of *n. magnocellularis* and *n. laminaris*.

Neurophysiological examination of these nuclei and a detailed analysis of the projections from *n. magnocellularis* to *n. laminaris* revealed the following properties. *N. magnocellularis* cells respond only to a narrow range of frequencies played to the ipsilateral ear. The cells display sharp excitatory tuning curves and primary-type response histograms, and always have a definable excitatory characteristic

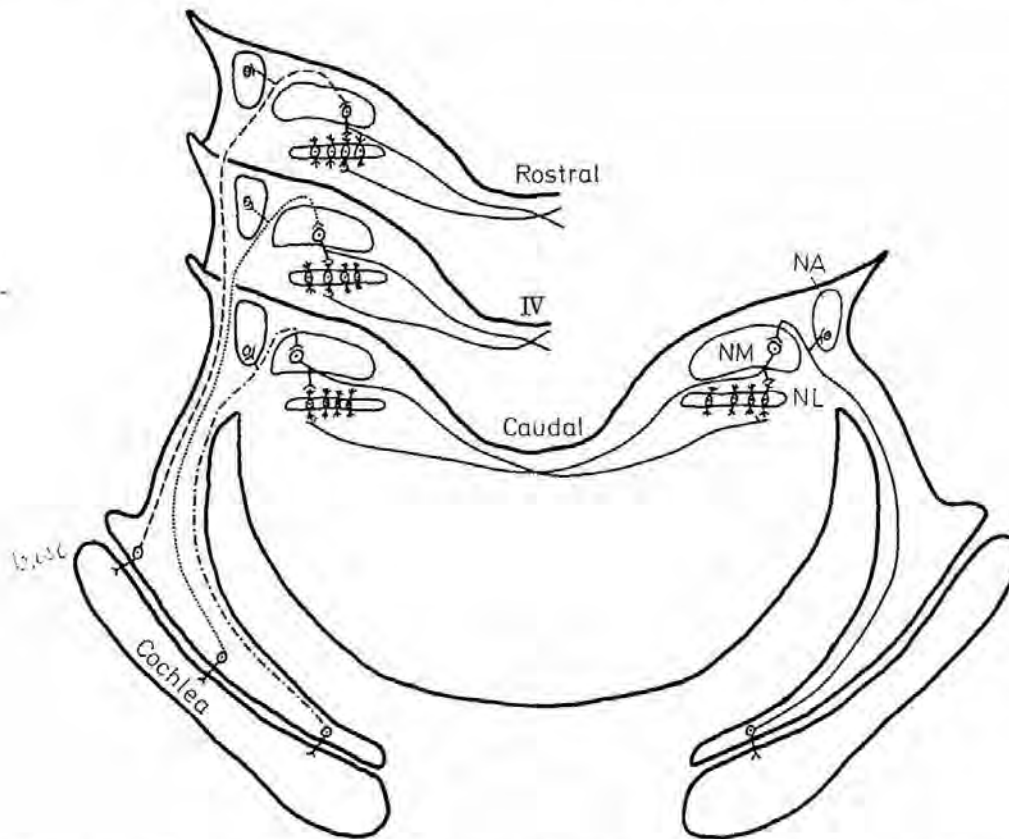


Fig. 10. Schematic drawing showing projections from cochlea via cochlear ganglion to *n. angularis* (NA) and *n. magnocellularis* (NM); and spatially segregated, bilateral projections from *n. magnocellularis* to *n. laminaris* (NL). IV—4th ventricle

frequency. The cells are organized in isofrequency columns, in which all cells respond to a similar characteristic frequency, and the physiologically-defined columnar organization corresponds to the anatomically observed cell columns. *N. laminaris* cells are binaurally activated by acoustic stimuli and usually show similar characteristic frequencies and thresholds to stimulation of each ear. That is, NL neurons are maximally activated by the same frequency range applied to either ear. In other respects their responses are similar to neurons of NM. The organization of neurons of both nuclei is characterized by a highly stereotyped and similar tonotopic organization; cells maximally responsive to low frequencies are situated in the caudolateral aspect of each nucleus and higher frequencies activate cells at progressively rostromedial positions. This tonotopic organization is sufficiently stereotyped that quantitative analyses of the relationships between the position of a cell in each nucleus and its characteristic frequency allows accurate prediction of this functional characteristic (within 200–400 Hz) from positional information alone. The utility of this finding is that it allows independent prediction of the characteristic frequency of a neuron, which can be compared to results obtained as a function of manipulations of an organism's acoustic environment.

Small lesions made in *n. magnocellularis* through tungsten microelectrodes after recording the characteristic frequency of cells in the lesioned area allowed further delineation of the organization of projections from *n. magnocellularis* on

one side of the brain to both laminar nuclei. Analysis of this tissue confirmed the spatial segregation of binaural projections onto each laminar nucleus (see Fig. 10). In addition, it was found that a lesion placed in a restricted portion of *magnocellularis* resulted in terminal degeneration in corresponding rostrocaudal and mediolateral positions in the two laminar nuclei. That is, there is a precise tonotopic and topographic projection from each region of *n. magnocellularis* to the dorsal side of ipsilateral *n. laminaris* cells and the ventral aspect of neurons in the corresponding position on the other side of the medulla. Furthermore, observations of Golgi-stained tissue have revealed that the dendrites of *n. laminaris* cells are confined to the glia-free margin surrounding the perikaryon lamina (see Fig. 13). These results allow precise delineation of the receptive cell surfaces of *n. laminaris* neurons as well as unusually precise specification of the source and functional properties of input to each dendritic surface of the neurons.

The morphogenesis of *n. magnocellularis* and *n. laminaris* was then investigated in several closely timed series of chicken embryos (RUBEL et al., 1976). The primary purpose of this investigation was to provide qualitative and quantitative baseline data describing the timing and extent of major morphogenetic events in the ontogeny of this neuronal network. Qualitative changes in nuclear structure were studied in Nissl- and silver-stained tissue from embryos between five days of incubation and hatching. The times at which *n. magnocellularis* and *n. laminaris* neurons pass through their final cycle of DNA synthesis ("cell birth-dates") were determined by ^3H -thymidine labeling. Finally, quantitative analyses of cell number and nuclear volume were conducted for each nucleus over the embryonic period from nine days of incubation through hatching.

The first major morphogenetic event to be considered in the analysis of any neural region is the developmental stage and duration of time during which cellular proliferation occurs. Cumulative labeling with ^3H -thymidine can be used to determine the time at which cellular proliferation has ceased and the occurrence of heavy labeling is a good indicator that the time of isotope injection was during one of the final mitotic cycles. Thus a thorough analysis by means of this technique allows one to estimate the period of development during which the cells of a given nuclear region pass through their final proliferative phase. Our analysis indicated that there is no overlap in the final period of DNA synthesis of NM and NL. NM cells consistently showed heavy labeling when injections were made at 60 hrs (2.5 days) of incubation and there was no indication of reliable thymidine uptake at 72 hrs of incubation. NL neurons, on the other hand, did not show heavy labeling unless the isotope was injected at 84 or 96 hrs of incubation. Figures 11 and 12 demonstrate these relationships in two animals, which were incubated together and treated identically except for the time of a single application of tritiated thymidine. Both animals were sacrificed at 17 days of incubation. Administration of ^3H -thymidine at 60 hrs of incubation (Fig. 11) produced heavy labeling of NM cells and relatively fewer grains over NL neurons, while application at 84 hrs (Fig. 12) resulted in heavy labeling of NL alone.

Summarizing the labeling experiments, it appears that the majority of NM neurons leave the mitotic cycle between 48 and 72 hrs of incubation, while the final production of NL cells is delayed by approximately one day. Both cell groups are produced in the region of the rhombic lip, and when first recognized in the embryo

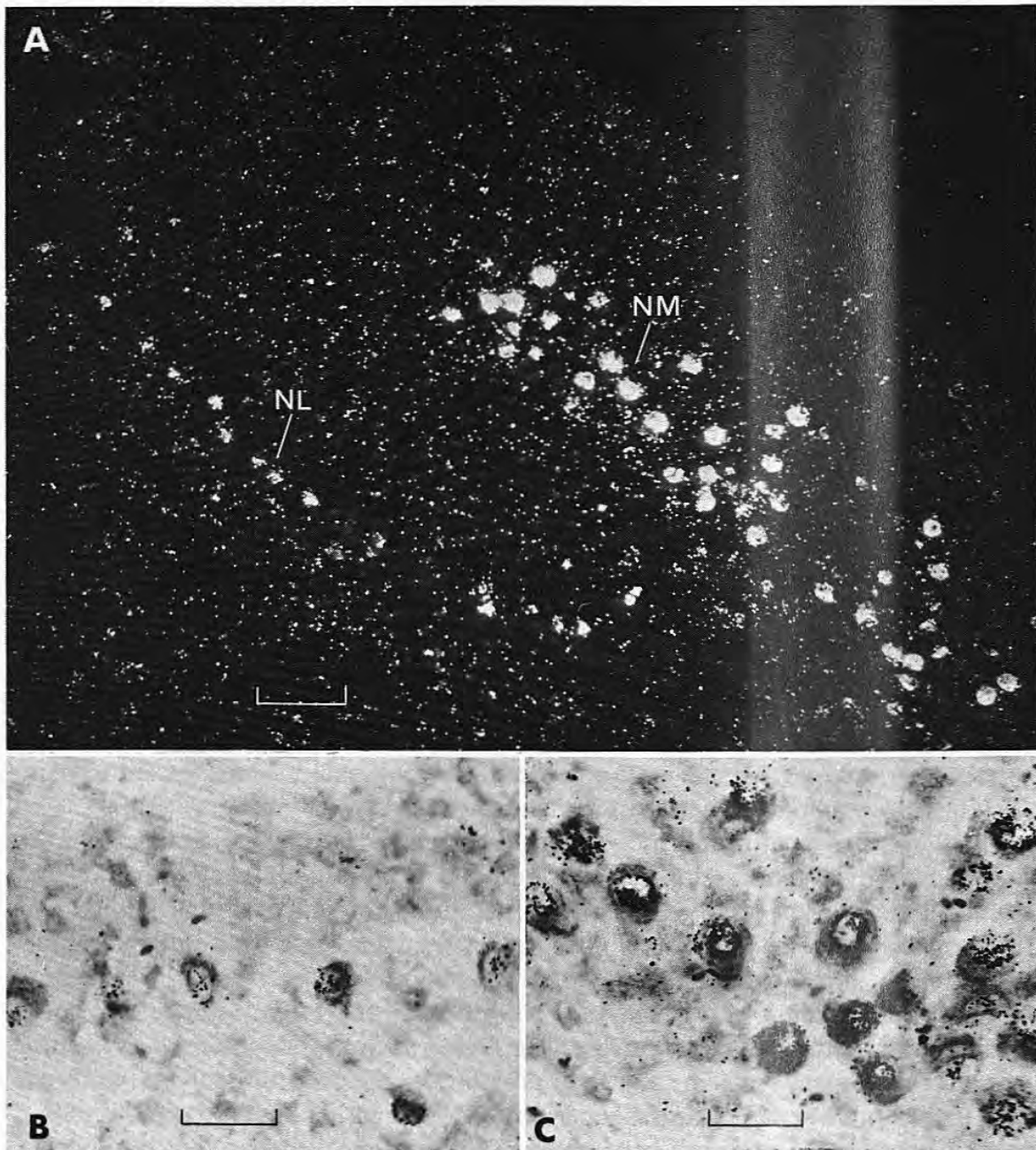


Fig. 11. (A) Autoradiograph of *n. magnocellularis* and *n. laminaris* as seen under darkfield optics. Tritiated thymidine ($25 \mu\text{Ci}$) was injected at 60 hrs of incubation, and animal was sacrificed at 17 days of incubation. *N. magnocellularis* cells are seen to be heavily labeled and *n. laminaris* cells are lightly labeled. Bar = $50 \mu\text{m}$. (B) Light-field photomicrograph of Nissl-stained *n. laminaris* cells, taken from same section as above. Silver grains are seen over nuclei of nearly all cells. Bar = $20 \mu\text{m}$. (C) Lightfield photomicrograph of Nissl-stained *n. magnocellularis* cells from same section, showing dense silver grains over the nuclei of cells. Bar = $20 \mu\text{m}$. (From RUBEL et al., 1976)

(about six days) they overlap throughout most of their rostrocaudal and mediolateral extent. It is therefore reasonable to hypothesize that both cell groups are produced by a single progenitor population, with NM cells being formed first and migrating away from the mother cells, and then, in a second wave of mitotic activity, the final population of NL cells being formed around 84–100 hrs of incubation. This temporal sequence of cellular proliferation, coupled with the fact

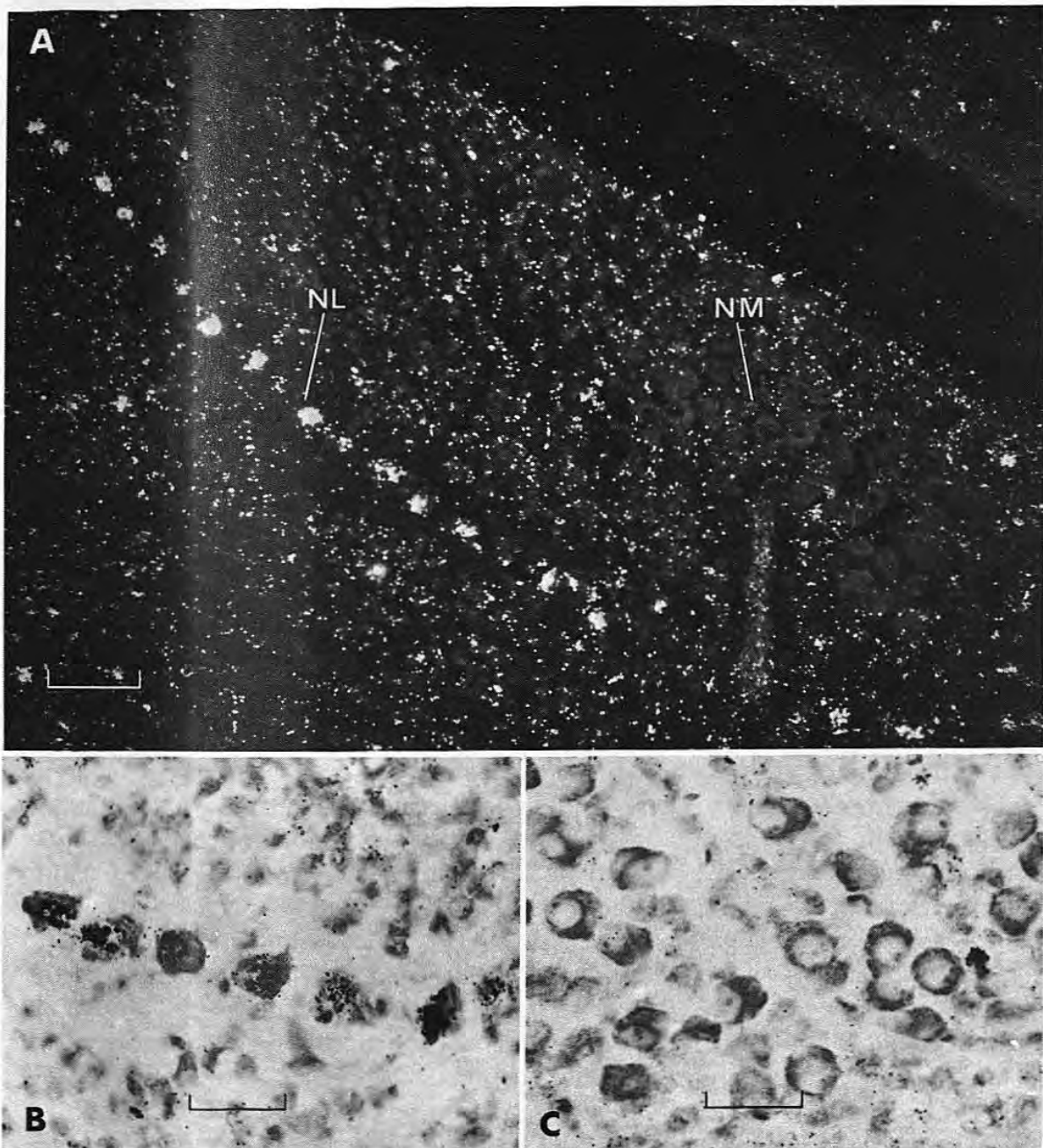


Fig. 12. (A) Darkfield photomicrograph of *n. laminaris* and *n. magnocellularis* showing result of tritiated-thymidine labeling at 84 hrs. Animal was from same group as that shown in Fig. 11, and was handled identically except for time of thymidine injections. *N. laminaris* cells can be seen to be heavily labeled, while *n. magnocellularis* neurons are not labeled. Bar = 50 μ m; (B) Lightfield photomicrograph of Nissl-stained *n. laminaris* cells taken from same section as above. Nuclei of cells show dense accumulations of silver grains. Bar = 20 μ m; (C) Lightfield photomicrograph of *n. magnocellularis* cells taken from same section. Few grains are seen over any cells, and labeling over cells of nucleus was no higher than background. Bar = 20 μ m. (From RUBEL et al., 1976)

that NL cells come to lie directly ventral to NM, suggests that the cells may interact during their proliferative or migratory phases. The hypothesis that presynaptic cells may influence proliferation or the early stages of differentiation of their postsynaptic target population has often been considered (e.g. see LAUDER and BLOOM, 1974). However, there is little evidence to support this conjecture and

no uniformity in the temporal sequence of proliferation of synaptically related cells. A more common finding is that cell groups that will later be in synaptic contact pass through one another during the migratory phase of development (ANGEVINE and SIDMAN, 1961; MIALE and SIDMAN, 1961; HANAWAY, 1967; COWAN, 1971; LANGMAN et al., 1971). This finding has led to the suggestion that cellular interactions during nerve cell migration may influence the pattern of synaptic connections that will later be manifest, or, as discussed earlier, may influence the migratory route of the nucleus through primitive protoplasmic processes. Little direct evidence for this hypothesis is available for central nervous system tissue, but we have observed in embryos around days 5–7 of incubation that cells labeled at the same time as NL cells can be observed streaming through the magnocellular nucleus. In any case, the occurrence and possible functions of such interactions might be particularly investigable in this system because it is known that there is a precise and relatively punctate topographic projection between the nuclei, which can be investigated morphologically or physiologically, and in addition, the two nuclei have nonoverlapping times of origin, which allows independent radiolabeling of either nuclear group.

Following proliferation and migration, these cell groups come to attain their stereotyped cytoarchitectural characteristics over the period from 9 to 15 days of incubation. By 9 days of incubation (Stage 34) both cell groups can be easily recognized although neither has assumed the cytoarchitectural or positional characteristics of later stages (Fig. 13A). At this time both nuclei are composed of relatively undifferentiated, densely packed cell bodies and there is no apparent subnuclear organization. In silver-impregnated tissue, it is apparent that the major afferent axons to both nuclei are present, although preliminary electron microscopic examination revealed no synapses at this time. Between days 9 and 13, major morphogenetic changes occur in both nuclei. The NM cells are displaced medially, cell density diminishes, and the cells become aligned into their characteristic columnar organization. The most striking changes occur in NL, where from the undifferentiated cluster of cells seen at day 9 a precisely defined monocellular or bicellular lamina, with a uniform glia-free margin, emerges by day 13 (Fig. 13B). This change begins in the rostromedial portion of the nucleus between days 9 and 11 and is completed in the caudolateral portion by around day 15.

Changes in cell number occur in both nuclei concurrently with these morphogenetic events (Fig. 14). Whereas NM loses only about 18% of its cellular population and all cell death appears to occur between embryonic days 11 and 13, cell death in NL is much more extensive (about 80%) and takes place over a considerably longer period (days 9–15). These changes in cell number are of interest for a number of reasons. First, while there are large differences in the amount and duration of cell death, the period of maximal cell loss in both nuclei is between 11 and 13 days of incubation. Since proliferation of NM and NL is separated by about 24–36 hrs, it appears that whatever factors regulate cell death may serve to bring the two nuclei into ontogenetic synchrony. Two such factors are the establishment of connections with an appropriate target population (COWAN, 1973; HAMBURGER, 1975) and the reception of afferent innervation (LEVI-MONTALCINI, 1949). Unfortunately, most experimental investigators of embryonic cell death have not been able to differentiate between these factors, because the



Fig. 13. (A) Nissl-stained section through *n. magnocellularis* and *n. laminaris* of 90-day chick. *N. laminaris* has not yet taken on its characteristic single-laminar appearance at this time; however, gli-free margin that surrounds it at later ages is already becoming apparent. Bar = 50 μm ; (B) Nissl-stained section of *n. magnocellularis* and *n. laminaris* at 13 days of incubation. *N. laminaris* can be seen surrounded by gli-free neuropil, with lateral division (left) 2—3 cells deep, and medial division a single-cell layer. Bar = 50 μm . (From RUBEL et al., 1976)

manipulations performed altered both the target population and the afferent input, the latter often transneuronally. In this respect, several factors suggest that these avian auditory nuclei may be particularly useful, namely: both nuclei are relatively small and well-defined; the periods of cell death and cell proliferation are widely separated in time; both afferent and efferent axons have formed before the time of cell death; and neurophysiological investigations are relatively routine in

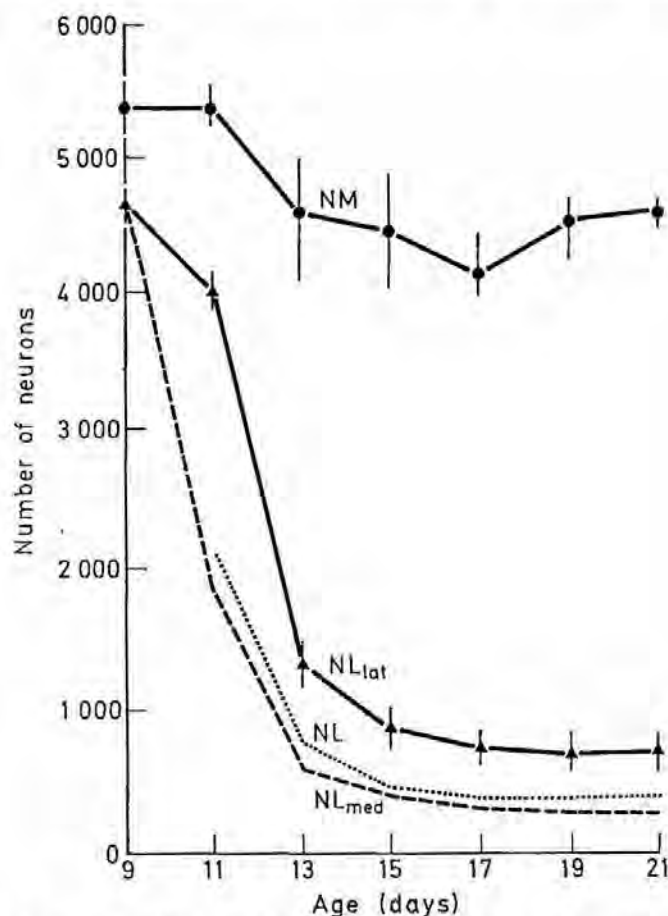


Fig. 14. Cell counts in *n. magnocellularis* and *n. laminaris* from 9 days to hatching. Points are means for each age, and vertical bars show ranges. Lines showing counts for divisions of *n. laminaris* are mean values. NM, *n. magnocellularis*; NL, *n. laminaris* (total); NL lat., lateral division of *n. laminaris*; NL med., medial division of *n. laminaris*

avian embryos, such that peripheral manipulations removing the major source of afferents to NM can be routinely accomplished without interfering with its efferent target, and the tectal target cells of NL can be removed embryonically without damaging their afferent innervation directly or transsynaptically. COWAN and his colleagues have made great contributions toward our understanding of embryonic cell death and have cautioned that for "further elucidation of the hypothetical relationships between cell death and the establishment of either afferent or efferent functional connections, it is necessary to know exactly when synapses are made, when functional activity emerges, and to be able to vary these factors in a systematic way" (ROGERS and COWAN, 1973). NM and NL of the chicken embryo appear to be the most suitable neuronal system in the vertebrate brain for accomplishing these goals.

The volumetric analyses of NM and NL (Fig. 15) also indicate a surprising amount of developmental synchrony in the enlargement of cell bodies and neuropil areas which occurs after the period of cell death. Since it is quite likely that functional connections are established by day 15, it will be important to understand the role that afferent activity may play in the regulation of this parameter as well. It is therefore important that the period of rapid cellular and neuropil expansions can be temporally separated from that of cell death.

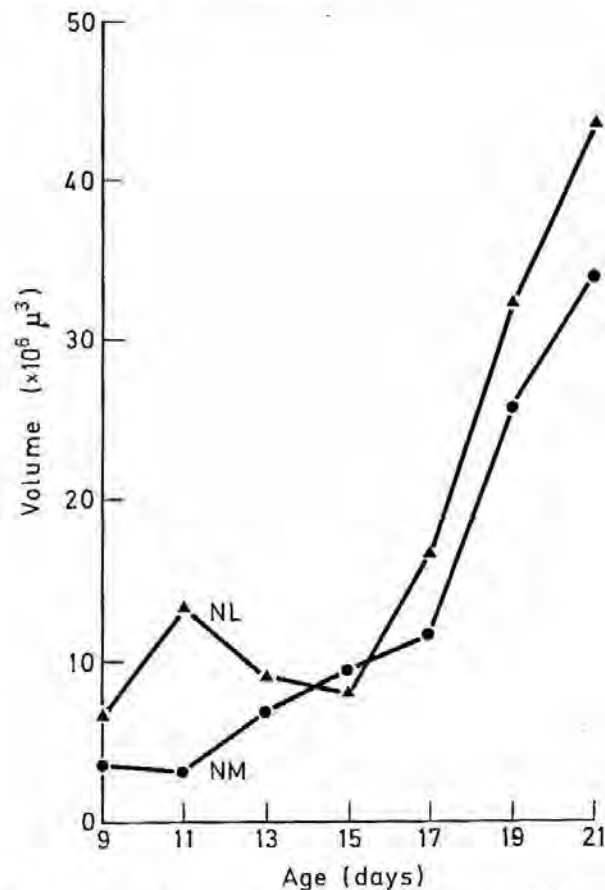


Fig. 15. Total volumes of *n. magnocellularis* and *n. laminaris* as function of age. NM, *n. magnocellularis*; NL, *n. laminaris*

Summarizing the ontogenetic information, *n. magnocellularis* (NM) and *n. laminaris* (NL) display the following important characteristics: i) The neurons of NM and NL go through their final phase of DNA synthesis over restricted and temporally separated time periods, which allows independent labeling of either neuronal population; ii) The period of cell death does not overlap with the proliferative period; iii) The alignment of NL cells is temporally correlated with, and possibly results from, cell death; iv) Cell loss occurs over a defined time period, has a definite spatial gradient (see Fig. 7) and, in the case of NL, is quite extensive; and v) Volumetric changes in cell bodies and neuropil regions occur in a period when functional connections are established and occur after the principal time of cell loss. These factors, in conjunction with the information on normal structural and functional connections, the accessibility of the avian embryo for surgery, neurophysiology, and pharmacology, and the potential for controlling embryonic and hatchling acoustic environment further suggest that these brain-stem auditory pathways will serve as an excellent preparation for investigations of cellular interactions in the developing nervous system.

Our first attempts at manipulating the cellular environment have used direct deafferentation. In one series of investigations (PARKS and ROBERTSON, 1976; JACKSON and RUBEL, 1976) the effects of removing the VIIIth nerve afferents either prior to synaptogenesis (otocyst removal) or well after (at hatching, three months, or three years) have been studied in *n. magnocellularis*. In support of LEVI-

MONTALCINI (1949) it was found that removal of the otocyst had little or no effect on magnocellularis cell number until the period of normal cell death, after which time both the amount and period of cell death were greatly enhanced. By 19 days of incubation, the deafferented *n. magnocellularis* had 40–50% fewer cells than the normal population. Surprisingly, this effect was not age-dependent; cochlea removal in hatchling, three-month-old, or adult chickens also resulted in a similar amount of transneuronal cell loss in *n. magnocellularis* within 45 days after surgery.

A second series of investigations (BENES et al., 1977) examined the degree to which transneuronal changes are specific to the postsynaptic membrane surface to which the input has been removed. By deafferenting one side of the NL cells it was possible to compare the deafferented dendritic surface with the other dendritic region of the same neurons, which had their normal input intact. An EM morphometric analysis indicated rapid and complete degeneration of the deafferented dendrites, while the opposite dendrites of these neurons retained their normal qualitative and quantitative characteristics.

While the above studies by no means answer the question of how both structural and functional characteristics of afferent input regulate neuronal ontogeny, it is hoped that progressively more subtle manipulations of afferent activity and increasingly sensitive measures of neuronal structure and function in this system will yield a more thorough understanding of how an organism's external environment regulates the ontogeny of neural networks.

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