PHARMACOLOGY *of* HEARING

Experimental and Clinical Bases

Co-Editors

R. DON BROWN, PH.D.

of Medicine in Shreveport

ERNEST A. DAIGNEAULT, PH.D.

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PREFACE

There are pharmacological agents that affect one or more of the basic physiological or biochemical processes involved in the perception of sound. These agents include potential neurotransmitter substances, drugs that alter synaptic physiology, those that affect energy transport, and the ototoxic agents, which produce a frank impairment in hearing. The purpose of this book is to review the emerging field of auditory pharmacology and place it in perspective with the many new developments in the anatomy, physiology, and biochemistry of hearing. A chapter on the pharmacology of audiogenic seizures is also included to (1) show how pharmacologic manipulation of hearing and/or central nervous system monoamines (norepinephrine, 5-hydroxytryptamine, and/or dopamine) results in the production of an animal model for the study of convulsive disorders and (2) give an insight into the interplay between the ascending auditory pathways and those pathways that are not normally considered to be functionally related to hearing. Furthermore, a number of drugs which affect hearing also alter equilibrium. Therefore, a chapter on vestibular pharmacology is included so that the similarities, as well as the differences, can be emphasized.

It is hoped that this volume will serve as a useful text for graduate students and researchers in otolaryngology, neurology, and auditory physiology and pharmacology as well as an important reference for the practicing clinician.

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Shreveport, Louisiana
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R. D. Brown
Ernest A. Daigneault

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CHAPTER 1

Anatomy of the Inner Ear

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1.1 INTRODUCTION

This chapter is being written from the perspective of a pharmacologist. Therefore one of its purposes is to furnish a description of the potential sites of action of drugs that affect hearing and/or equilibrium and to describe the accessibility of those sites to drugs.

Its other purpose is to provide the reader with sufficient background to interpret the material presented in subsequent chapters. It is not intended to be an in-depth survey of the anatomy of the inner ear; these details can be found in publications by authorities in this area.[1–13]

1.1.1 Gross Anatomy

The inner ear (labyrinth) lies within the petrous portion of the temporal bone and consists of the cochlea and vestibular apparatus. This entire structure is a series of interconnected bony cavities (osseous labyrinth) within which lie a number of communicating membranous sacs and ducts (membranous labyrinth). The fluid filling the space between the osseous and membranous labyrinths is perilymph (Figure 1.1), which has a composition similar to that of extracellular fluid; it is apparently formed by an influx of cerebrospinal fluid and by ultrafiltration from the vessels lying in the tissue covering the inner walls of the osseous labyrinth.[14] The potassium-rich fluid within the membranous labyrinth is endolymph (Figure 1.1), which is similar to intracellular fluid in ionic composition. This fluid is thought to originate from the stria vascularis of the cochlea and the differentiated, nonsensory epithelia of the vestibular apparatus.[6,15] The fluid surrounding the sensory receptors (hair cells) of the cochlea and vestibular apparatus is isolated from endolymph by tight junctions on the epithelia lining the endolymphatic compartment.[16]

1.1.2 Microscopic Anatomy

The cochlea is a coiled, fluid-filled tube encased in a bony capsule. The two outer fluid compartments, the scala vestibuli and scala tympani, are connected by the helicotrema, an opening at the apex of the cochlea (Figure 1.1). The central compartment, the scala media, is roughly triangular and is bounded by Reissner's membrane, the basilar membrane, and the stria vascularis (Figure 1.2). The organ of Corti rests on the basilar membrane and includes one row of inner hair cells, three rows of outer hair cells, supporting cells (Deiters, Hensen, and Claudius), the rods, pillars, and tunnel of Corti, the pillar cells, the afferent and efferent nerve endings, and the basilar and tectorial membranes. The enclosure formed by Reissner's membrane and the basilar membrane is called the cochlear duct or cochlear partition. (Some investigators exclude the organ of Corti from the cochlear duct by defining the tectorial membrane rather than the basilar membrane as one of the

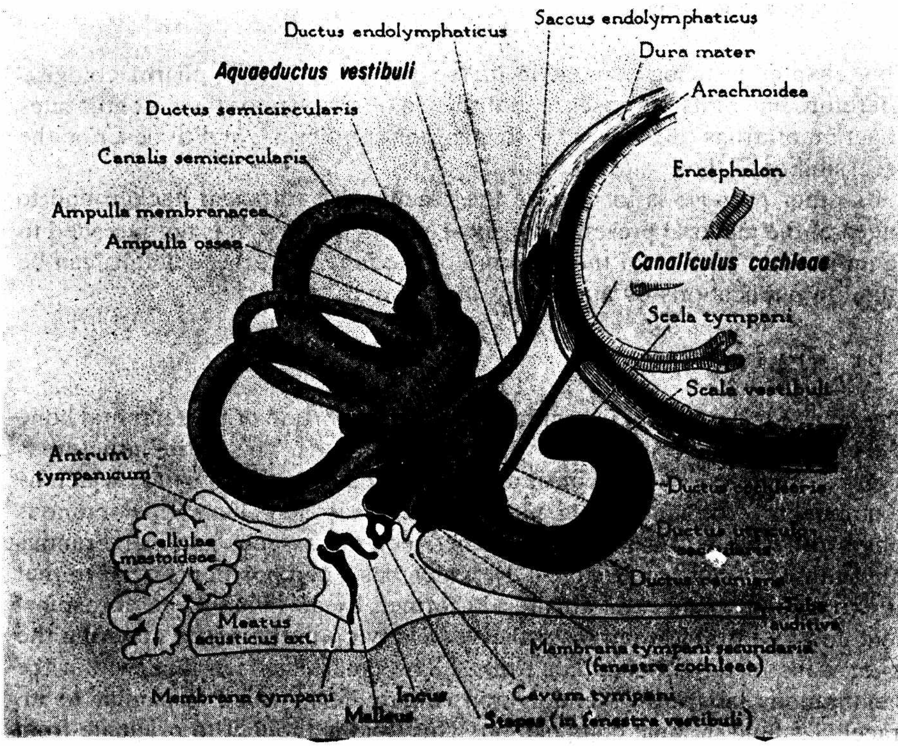

Figure 1.1 Schematic representation of the vestibular and cochlear aqueducts in relation to the labyrinthine systems for endolymph and perilymph (perilymphatic compartment darkest shade). Reproduced by permission from Anson et al.[1]

boundaries of the cochlear duct.) The superior surface of the hair cells, the framework of supporting cell processes that holds them in place, and the superior aspects of the rods of Corti constitute the reticular lamina of the cochlea. Running up through the center of the coiled tube of the cochlea is the modiolus, which contains the spiral ganglia (nerve cell bodies of the primary auditory afferents) and the intraganglionic spiral bundles (axons of the cochlear efferents). Cochlear afferent and efferent nerve fibers penetrate the temporal bone through the habenula perforata and take one of several courses to the sensory epithelia. (These courses are described later in detail.)

The vestibular apparatus contains several specialized areas of epithelia: the ampullar cristae and the saccular and utricular maculae. The lining of the endolymphatic compartment is a one-layered epithelium, below which is a layer of connective tissue. Most of the epithelial lining is undifferentiated and squamous. In the areas of specialization, however, the epithelium is differentiated into a secretory epithelium and a sensory epithelium.[6] The epithelium and connective tissue stroma which line the endolymphatic com-

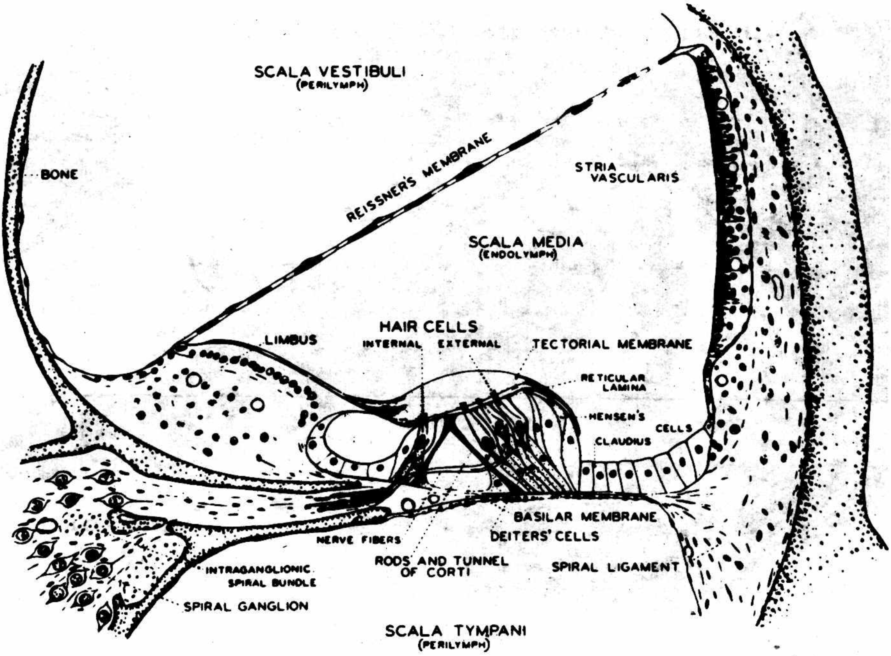

Figure 1.2 Cross section of the second turn of the guinea pig cochlea. Reproduced by permission from Davis et al.[13]

partment are secured to the outer boundary of the perilymphatic compartment by loose connective tissue (Figure 1.3); there are no vestibular structures analogous to Reissner's and the basilar membranes of the cochlea. The nerve cell bodies of the vestibular afferents constitute Scarpa's ganglion and are located in the bony capsule that surrounds the labyrinth. Vestibular afferent and efferent fibers penetrate the temporal bone through the cribrose macula and course directly to the sensory epithelia (Figure 1.3).

1.2 DRUGS AND THE INNER EAR

1.2.1 Distribution

Several factors govern the distribution of drugs within the fluid compartments of the inner ear and, as a result, their accessibility to the sensory receptors and associated nerve endings. Figure 1.1 shows that gross anatomical connections exist between the cochlea and vestibular apparatus for the endolymphatic and perilymphatic fluid compartments. On closer examination, however, the endolymphatic compartment is found to be discontinuous. The endolymphatic connection between the saccule and utricle is

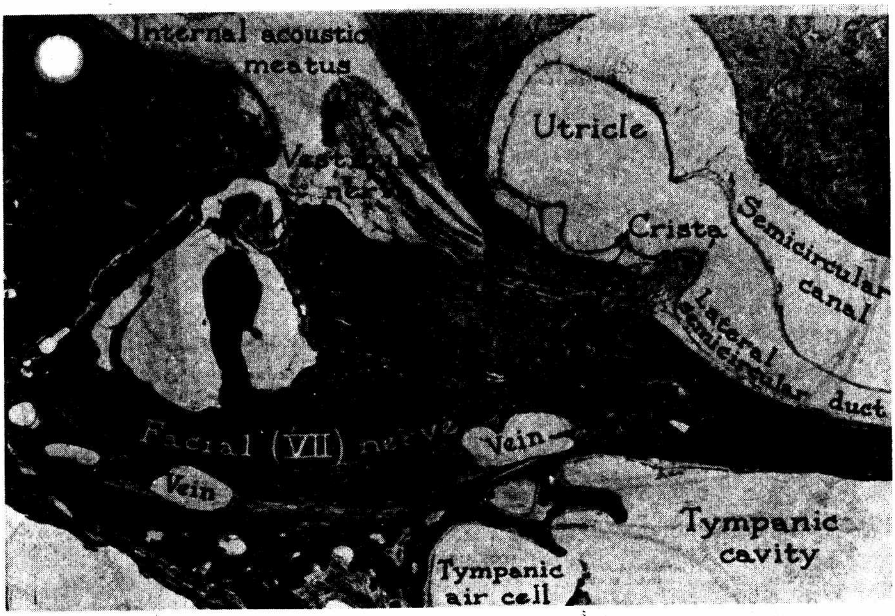

Figure 1.3 Utricle and portion of lateral semicircular canal with its crista. Reproduced by permission from Anson and Donaldson.[7]

very small in most animal species and in some cases is closed by a valve on the utricular side of the endolymphatic duct; furthermore, endolymph circulation in the vestibular apparatus is separate from that in the cochlea.[17] Thus it does not appear likely that drugs that enter the endolymph of the cochlea or vestibular apparatus would be distributed by it to the other system. (It should be recognized, however, that hydrostatic pressure changes in disease states can be reflected through both systems, as it is in Meniere's disease.[18-19])

In contrast, the perilymphatic fluid compartment of the cochlea does appear to be continuous with that of the vestibular apparatus.* Furthermore, it has been proposed that cortilymph, the interstitial fluid within the organ of Corti proper (Figure 1.2), is similar to perilymph in ionic composition and is continuous with the perilymph of the scala tympani.[14] In the vestibular apparatus there is no structure analogous to the basilar membrane that might limit access of perilymph to the vestibular sensory epithelia. Therefore drugs that gain access to the perilymphatic fluid could be distributed throughout

*In some animals, notably the guinea pig, a connective tissue boundary membrane divides the perilymphatic compartment into vestibular and cochlear divisions.[11] Even in this animal, however, it is unclear whether an anatomical communication exists between the two divisions, and there is no proof that this membrane serves as an effective diffusion barrier to ions, nutrients, or drugs.

that compartment and conceivably to the cochlear and vestibular sensory receptors and their nerve endings.

The stria vascularis of the cochlea appears to form another compartmentalized area of the inner ear (Figure 1.4).[16] Diffusion or active transport of drugs into this compartment may explain the selective cochlear toxicity of the loop diuretics. These drugs exert their initial action on the stria vascularis of the cochlea.[20] On the other hand, the secretory epithelium, the analogous tissue of the vestibular apparatus, is not compartmentalized; this could account for the relative lack of vestibular toxicity of the loop diuretics.

Another way for drugs to gain access to the area of the receptors is by passive or active transport from the capillary beds of the vascular system that supplies those specific areas; that is, the arterioles of the basilar membrane of the cochlea and the arterioles that serve the ampullae and the utricle and saccule. A blood-cochlea barrier is present, however (Figure 1.4). This barrier seems to be similar to the "blood-brain barrier"[21-22] and most certainly plays an important role in determining which drugs find their way into

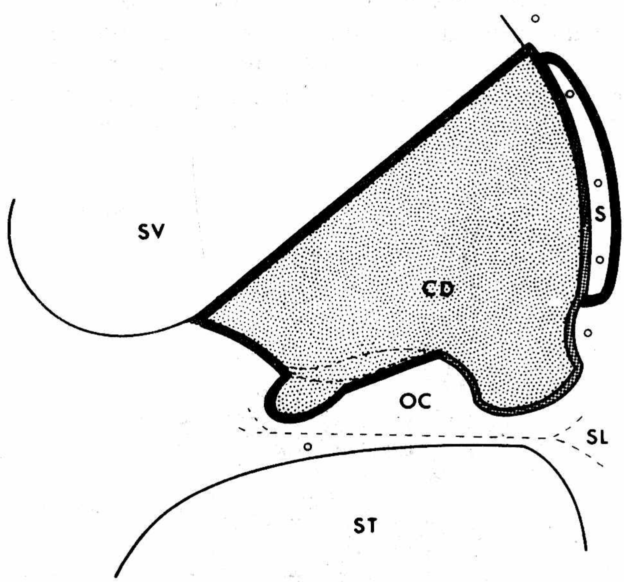

Figure 1.4 The perilymph-endolymph barrier of the cochlea and the stria vascularis. This diagram summarizes the results of observations on tight junctions that seal the cochlear duct and the intercellular spaces of the stria vascularis. SV = scala vestibuli, ST = scala tympani, CD = cochlear duct, OC = organ of Corti, S = stria vascularis, SL = spiral ligament. All nonsensory epithelia, which line the cochlear duct, have zonulae occludentes of the intermediate to tight type (dotted line). In contrast, the zonulae occludentes of the cochlear sensory epithelium and junctions of basal cells of the stria vascularis are very tight (thick black line). The circles represent blood vessels, all of which have tight junctions such that their nonfenestrated endothelia also form barriers. Reproduced by permission from Jahnke.[16]

the cochlea. (It is not known whether a similar barrier exists in the vestibular portion of the inner ear.)

1.2.2 Possible Sites of Action

Logical sites of action of drugs within the inner ear include (1) the sensory receptors (mechanoreceptors; i.e., hair cells), (2) their afferent and/or efferent nerve endings, (3) the stria vascularis of the cochlea and/or the analogous structure of the vestibular apparatus, and (4) the vasculature of the cochlea or the vestibular apparatus. (In addition, the brainstem is the presumed site of action of antimotion sickness drugs; this, however, is discussed in Chapter 11).

Hair Cells

Two types of mechanoreceptor are found in the cochlea and the vestibular apparatus, each with a different basic shape and pattern of innervation (Figures 1.5 and 1.6). Both types of hair cell possess stereocilia and it is thought that their mechanical distortion initiates the transduction processes of the inner ear. The Type I hair cell is flask-shaped and synapses directly with afferent fibers. In contrast, the efferent fibers synapse with the afferent dendrites rather than with the hair cell itself. The inner hair cell of the

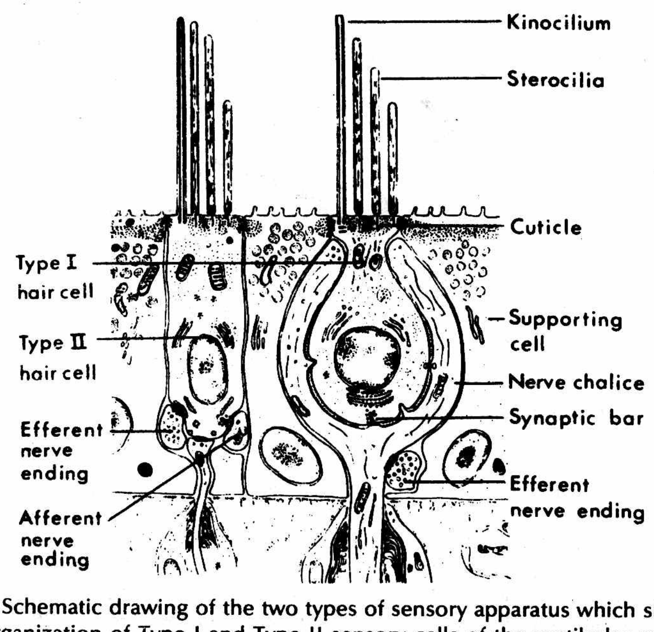

Figure 1.5 Schematic drawing of the two types of sensory apparatus which show the fine structure organization of Type I and Type II sensory cells of the vestibular apparatus and their innervation. Reproduced by permission from Wersall and Bagger-Sjoback.[6]

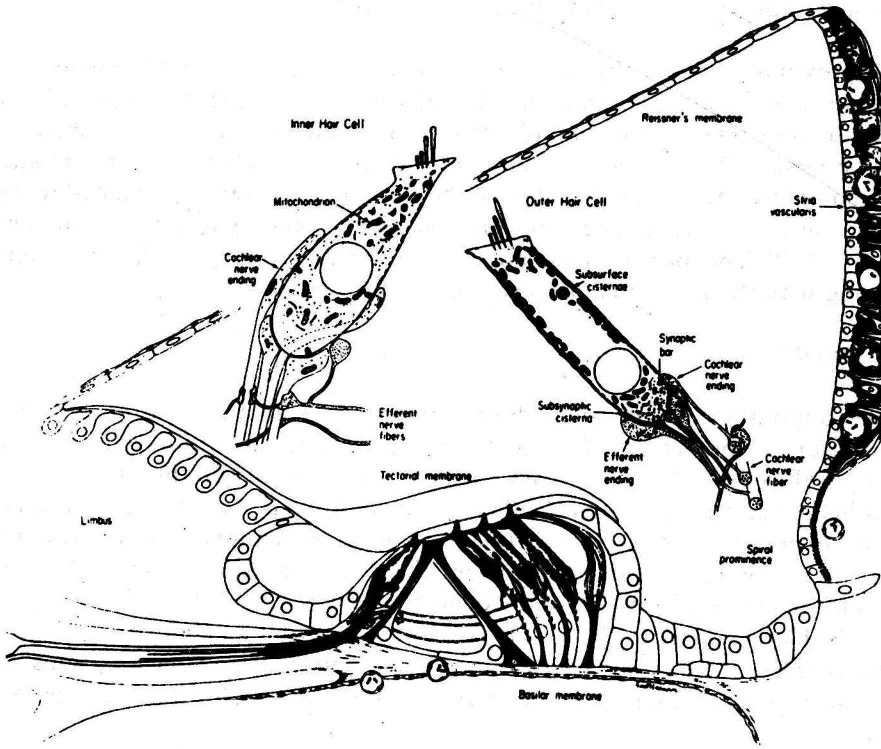

Figure 1.6 Drawing of the cochlear duct, second turn, guinea pig cochlea. Only recent findings are shown in detail. Reproduced by permission from Smith.[5]

cochlea and the vestibular hair cell with the afferent nerve chalice are Type I hair cells. The Type II hair cell is cylindrical and has direct synaptic contact with the afferent and efferent nerve terminals. The outer hair cells of the cochlea and the vestibular hair cells which lack the afferent nerve chalice are Type II hair cells. The aminoglycosides seem to produce their ototoxicity primarily by direct action on the hair cells, selective cochlear and/or vestibular toxicity being dependent on the specific aminoglycoside.

Afferent and Efferent Synapses

The morphology of the afferent and efferent synapses of the inner ear is presented later in this chapter and the physiology and pharmacology of these synapses are subjects of subsequent chapters. It should be pointed out at this juncture, however, that alteration of afferent and/or efferent synaptic physiology, due to direct action on these synapses, has not been demonstrated as an important part of any drug's therapeutic or toxic effect.

Stria Vascularis and Vestibular Secretory Epithelia

As previously stated, the stria vascularis of the cochlea and the analogous tissue of the vestibular apparatus (the differentiated, nonsensory epithelium) are the apparent sources of endolymph. The stria vascularis is also thought to be responsible for the generation of the positive cochlear endolymphatic dc potential; the analogous tissue of the vestibular system is presumed to be the source of the smaller, positive vestibular endolymphatic dc potential.[10,20,23-24] The loop diuretics appear to exert their ototoxic effect by interfering with the functions of these specialized, secretory tissues.

Vasculature

The labyrinthine or internal auditory branch of the anterior inferior cerebellar artery, a branch of the basilar artery, supplies the entire membranous labyrinth (Figure 1.7). The main cochlear artery spirals up through the modiolus and serves most of the cochlea by breaking up into many arterioles that feed capillary beds for the pertinent cochlear structures. The rest of the cochlea, the basal portion, is supplied in an analogous fashion by the cochlear ramus of the vestibulo-cochlear artery.[11-12]

The blood supply to the vestibular apparatus is not so complex as that of the cochlea. It consists primarily of capillary beds formed beneath each area of specialized epithelia by arterioles and venules which follow the nerves

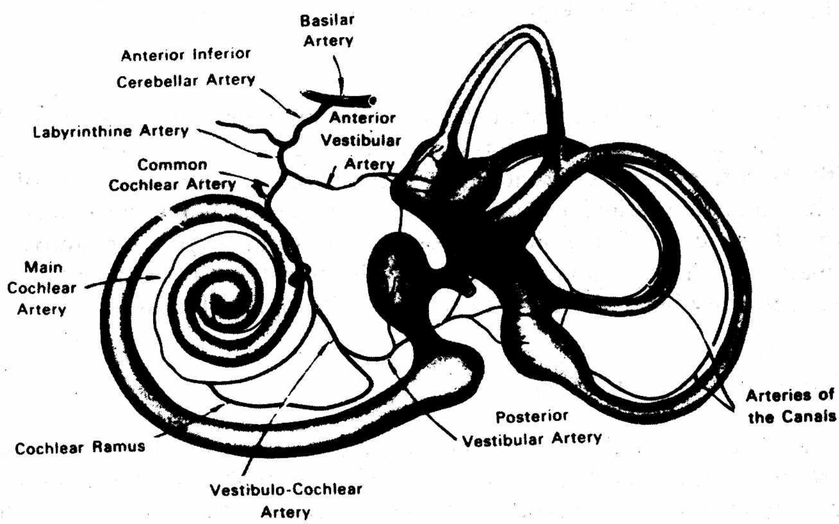

Figure 1.7 Diagrammatic sketch which shows the arterial system of the mammalian membranous labyrinth. Reproduced by permission from Schuknecht.[11]

that supply these structures. A separate, loosely connected set of capillaries is formed by arterioles and venules that extend throughout the connective tissue which forms the outer boundary of the vestibular division of the perilymphatic fluid compartment.[11]

The vasculature of the inner ear has been postulated as the site of action involved in the ototoxicity of nonsteroidal antiinflammatory agents and quinine.[20] In addition, disruption of the blood supply to the inner ear by a clot is thought to be responsible for the sudden hearing loss that has occurred in females who take oral contraceptives; vasodilator therapy has been given in an attempt to restore their cochlear circulation to normal.[25]

1.3 AFFERENT AND EFFERENT SYNAPSES OF THE INNER EAR

The morphology of the synapses in the inner ear is similar to that of other synapses that are chemically mediated.[9,26] Two types of receptoneural synapse occur: the afferent are found on Type I and Type II hair cells (Figures 1.5 and 1.6). The other receptoneural synapse occurs primarily between Type II hair cells (e.g., the outer hair cell of the cochlea) and their efferent nerve terminals (Figures 1.5 and 1.6); only rarely does an efferent terminal make contact with a Type I hair cell.

A third type of synapse occurs in the region immediately beneath the Type I hair cell between vesiculated enlargements of the efferent fibers and the afferent dendrites coursing from the cell (Figures 1.5 and 1.6); only rarely is it found in the region beneath the Type II hair cell.

The most recently discovered synapse is the dendro-dendritic. So far this synapse has been identified only in the cochlea and is apparently confined to synapses between the afferent dendrites that innervate the outer hair cells. Bodian[26] states that these junctions "between pairs of presumptive afferent processes suggest the possibility of dendro-dendritic interaction confined to the outer hair cell system."

Finally, it must be pointed out that an anatomical substrate has not been conclusively identified for the much speculated-about functional interaction between cochlear inner and outer hair cells. (See Chapter 2 for further discussion.) The only candidates for this role at the present time are the atypical, desmosomelike junctions in the spiral ganglion reported by Adamo and Daigneault.[27]

1.4 INNERVATION OF THE COCHLEA

This portion of the chapter is restricted to a general description of the innervation of the cochlea. Details of the innervation of the vestibular apparatus are presented, as needed, in Chapter 11.