3
Surgical Pathology

Cochlear implants invade the inner ear and thus have the potential to produce complications. An electrode array implanted into the inner ear could result in degeneration of residual auditory nerve fibers, and predispose to middle ear infection extending to the cochlea and even the meningeal linings of the brain. Furthermore, with a profound hearing loss there could be too few residual hearing nerves in the cochlea to be stimulated for speech understanding. Implants in infants and young children introduced a new set of concerns, in particular the effect of head growth on the device and the effect of the device on head growth, as well as the increased risk of inner ear infection because of the high incidence of otitis media in young children. The effect of electrical stimulation per se could be damaging in the adult and child, and is addressed in Chapter 4.

The pathological effects of cochlear implantation should be kept to a minimum, as advanced speech-processing strategies would require an adequate population of neurons for good sound fidelity. Strategies might use residual hearing in association with direct electrical stimulation of the auditory nerve.

This chapter addresses specific pathological issues of importance for cochlear prostheses. The first is electrode insertion trauma and the histopathological consequences. The second is the biocompatibility of the device, including screening studies of candidate biomaterials and the assembled prosthesis. The third is infection of the middle ear and the risk of it spreading to the cochlea and meninges. This possibility is perhaps the most important issue for the safety of cochlear prostheses in children. The most common microorganisms associated with middle ear infections are summarized, and the development of suitable animal models discussed:

Inflammation

Inflammation is a response by the tissues of the body to an agent that is damaging, such as physical insults, chemicals, and toxins produced by bacteria. It is a defense mechanism to help nullify and contain the effects of the damaging agent.

Classification

Initially, there is an immediate response or acute phase, with the exudation of fluid and plasma proteins from the blood, as well as the emigration of white cells or polymorphonuclear leukocytes (in particular the neutrophils) through the smallest of the veins (venules). On the other hand, if healing does not happen and the agent persists, the inflammatory response will become subacute, and may pass into a chronic phase. In the subacute phase there are still signs of the initial inflammatory response, but this changes to one of containment and the development of fibrous tissue. In the chronic phase there is an accumulation of the white cells referred to as lymphocytes and macrophages, as well as the development of fibrosis and calcification and even new bone formation.

Etiology

Inflammation may be due first to the release of agents due to physical trauma. Second, chemicals can be released from the polymers used to make the implant or electrode. In this case the catalyst that polymerizes the filler may be toxic and exert its effects through leaching from the material. This was the case with stannous octoate used for some silicone rubbers (Clark 1987). Metals or ceramics used in the implant must also be checked to ensure that they have no deleterious effects. Third, bacteria may infect the tissue in the inner ear at the time of implantation, or extend into the inner ear from a middle ear infection. They exert their effect through the release of toxins. These toxins may be actively produced (exotoxins) or passively with the destruction of the bacterium (endotoxins).

Pathophysiology

Inflammation, as stated, is the body's response to a harmful agent. It destroys, dilutes, or walls off the agent. It also sets off a series of changes leading to healing and reconstitution of the tissue when possible. With repair, which begins during the early phase of the inflammation, the damaged tissue is replaced through regeneration from native cells, and/or the area is filled with fibrous or scar tissue.

With acute inflammation, agents (histamine, bradykinin, substance P) released as a result of the noxious agent, act on the wall of the venules, causing them to dilate and allow the passage of blood proteins through the wall. The released proteins include antibodies to counteract an infection. If the injurious agent is more severe, capillaries and small arteries may also become dilated.

Once released into the tissue, the white cells (neutrophils) migrate toward the site of injury down a chemical gradient. The white cells move when the chemically attracting agents act on cell membrane receptors, and this leads to the release of calcium ions into the cytoplasm that cause contractile movements in the cell (Snyderman and Uhuig 1992). Once arriving at the site of the inflammation, the white cells destroy bacteria through the process of phagocytosis (Fig. 3.1). This involves three distinct steps: (1) recognition and attachment of the particle,

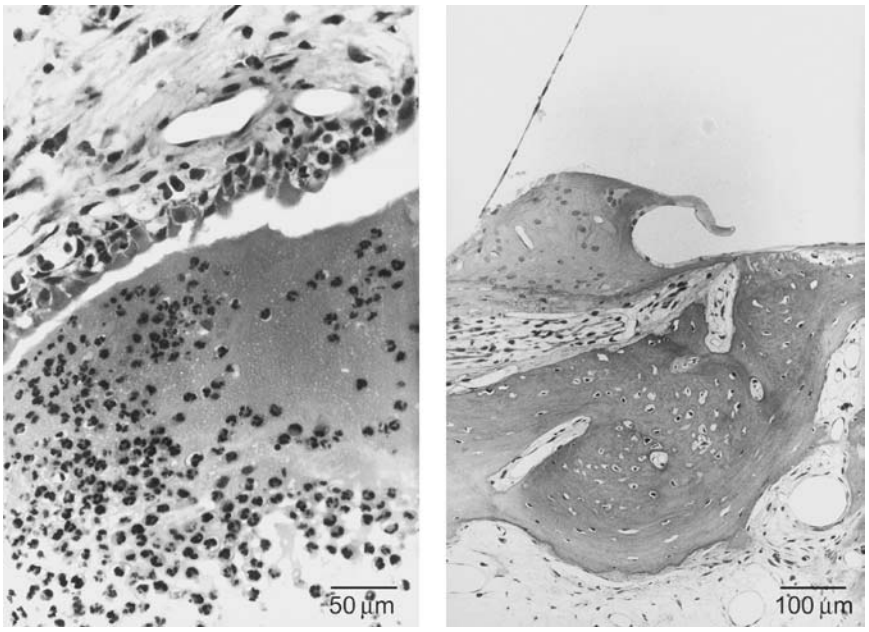

FIGURE 3.1. Left: Acute inflammation in the cochlea with the presence of polymorphonuclear leukocytes (neutrophils). Right: Chronic inflammation with the development of fibrous tissue and new bone. New bone is particularly prone to occur beneath the spiral lamina.

(2) engulfment and inclusion in a vacuole in the cytoplasm, and (3) killing or degradation of the material.

With chronic inflammation there is infiltration with mononuclear white cells that include macrophages, lymphocytes, and plasma cells in response to persistent injury. There may be tissue destruction, and there is an attempt at healing through the proliferation of small blood vessels and the formation of fibrous tissue. The macrophage is the main cell initiating chronic inflammation. It is derived from monocytes that come from the bone marrow. The monocytes begin to migrate early in inflammation, that is, within the first 48 hours, and their spread into the tissue (extravasation) is governed by the same factors affecting the neutrophil white cells. Once in the tissue, the monocyte is transformed into a macrophage. The macrophages carry out phagocytosis and when activated produce fibrous tissue. Lymphocytes are also mobilized with continuing inflammation and together with plasma cells produce antibodies to infection.

Chronic inflammation may lead to the formation of not only fibrous tissue but also new bone (Fig. 3.1). The bone may arise from the actual bone of the organ (i.e., cochlea) when it is referred to as orthotopic, or it can come from the fibrous tissue. New bone formation is part of the healing phase in the tissue after physically and chemically induced inflammation. Bone formation commences in cal-

cified tissue. Calcification results when calcium phosphate crystals are deposited in the tissue as an apatite. The process occurs in two phases: (1) initiation, and (2) propagation. They take place both intracellularly and extracellularly (Majno and Joris 1996). The initiation of intracellular calcification occurs in the mitochondria of the cells through the accumulation of calcium. The initiators of extracellular calcification are phospholipids bound to the membranes of vesicles. The calcium is concentrated in these vesicles through a series of biochemical steps. The propagation of the calcification depends on the concentration of calcium and phosphate ions as well as the presence of facilitating and inhibiting proteins in the extracellular space. These matrix proteins facilitate the interaction of the minerals and the cells to produce calcification in tissue that is then referred to as osteoid. There is phase delay of some days before bone formation commences in the osteoid tissue.

Bone formation commences with the activation of cells (osteoprogenitor cells) to produce osteoblasts and osteocytes. Their generation is regulated by cytokines and growth factors such as fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), insulin-like growth factor, and transforming growth factor-β (TGF-β) (Mundy 1995). The osteoprogenitor cells are pluripotential mesenchymal stem cells located in the vicinity of all bony surfaces. When stimulated they undergo cell division and produce offspring that differentiate into osteoblasts. A specific transcription factor stimulates osteoblast specific gene expression. The osteoblasts synthesize, transport and arrange the many proteins of the matrix, and initiate further mineralization. They have cell surface receptors that bind many hormones to regulate activity, for example, parathyroid hormone, vitamin D, cytokines, and growth factors. Once the osteoblasts become surrounded by the matrix, they are known as osteocytes. The osteocytes communicate with each other via processes passing along an intricate network of tunnels in the matrix known as canaliculi. These processes transfer surface membrane potentials and substrates. Bone formation is an interplay between deposition and removal. The osteoclast is responsible for bone absorption, and is derived from hematopoietic progenitor cells that also give rise to monocytes and macrophages. Cytokines too are crucial for osteoclast differentiation and maturation, and these include interleukins, tumor necrosis factor, and granulocyte-macrophage colony-stimulating factor. These cells are multinucleated and the result of fusion of mononuclear nuclear precursors. They are intimately related to the bone surface, and form a localized seal around the surface of the bone. A hydrogen pump in the cell acidifies this localized area, and the regional bone is dissolved. The osteoclast also releases into the space a multitude of enzymes that help disassemble the matrix proteins into amino acids and liberate and activate growth factors. Thus as bone is broken down to its elemental units, substances are released that initiate its renewal. The proteins forming the matrix of bone are primarily type 1 collagens as well as other proteins from osteoblasts. The osteoblasts deposit the collagen for the matrix in a random weave know as woven bone or in an orderly layered manner referred to as lamellar. Woven bone is formed more quickly.

Insertion Trauma

Physical injury damages the cochlea through tears of the basilar membrane and fractures of the spiral lamina in particular, and this also induces an inflammatory response. The pathological responses of tissue to trauma are discussed in this chapter. The effects of the pathological changes induced by specific types of electrodes are described in the section on bioengineering in Chapter 8.

Tissue Responses in the Cochlea of the Experimental Animal

The effects of surgical trauma on the tissues in the cochlea can be studied in the experimental animal. The cat has been the model for most studies on the effects of injury to specific cochlear tissues. But the monkey cochlea is more similar to that of the human, and does not narrow markedly 6 to 7 mm from the round window, as occurs in the cat. Therefore, it has been more useful in studying the effects of different electrode designs.

Hair Cell Preservation

Hair cells were preserved in the cat and monkey cochleae implanted with scala tympani electrodes with and without electrical stimulation, unless there was infection or trauma to the basilar membrane and the spiral lamina in particular (Shepherd et al 1983b). In the studies by Shepherd et al (1983a,b), three quarters of the inner and outer hair cells were well preserved. Atrophy of hair cells in the organ of Corti was generally confined to the lower basal turn adjacent to the electrode array. Chronic electrical stimulation per se, did not contribute to the loss of hair cells. In addition, the preservation of spiral ganglion cells and the auditory nerve was associated with hair cell survival. This was consistent with the release of trophic factors from the hair cells for the health of the auditory neuron. In the cochleae, where there was widespread loss of hair cells, this was associated with severe inflammation. The preservation of hair cells in the cat was also seen by Xu et al (1997) in their study on the long-term effects of intracochlear electrical stimulation using high rate biphasic electrical pulses. An increase in the click-evoked auditory brainstem response (ABR) threshold was found following implantation in all cochleae, but recovery to near-normal levels occurred in approximately half of the stimulated cochleae. Frequency-specific stimuli indicated that the most extensive hearing loss occurred in the high-frequency or basal region of the cochlea (12,000 and 24,000 Hz) adjacent to the stimulating electrode. Thresholds at lower frequencies (2000, 4000, and 8000 Hz) appeared at near normal levels. There was no evidence of cochlear damage caused by high-rate electrical stimulation.

Physiological and psychophysical studies in the experimental animal have also demonstrated that functioning hair cells were present after cochlear implantation (Clark, Kranz et al 1973). The behavioral study by Clark, Kranz et al (1973) on cats showed that “electrophonic” hearing could be found in the chronically im-

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