Only four patients in the study by Yang et al. had objective tumor responses to the anti-VEGF antibody, which is consistent with emerging data suggesting that VEGF inhibition alone is unlikely to cause regression of established, mature blood vessels. Challenges lie ahead for the design of clinical trials if disease stabilization, rather than tumor regression, becomes the norm for what may be achieved with antiangiogenic agents. Laboratory studies suggest, however, that dual inhibitors of endothelial cells and pericytes might, in contrast to inhibitors that act exclusively on VEGF, cause regression of established lesions. In this regard, it might be a fortunate coincidence that many kinase-domain–related inhibitors that are under development also inhibit the PDGF receptor, which is important for the growth and survival of pericytes. In addition, knowledge of the function of pVHL would support combining antiangiogenic agents with agents that interrupt specific tumor-cell autocrine loops (such as that created by TGF-α and its receptor, epidermal growth factor receptor).

Definitive phase 3 studies will now be required in order to ascertain the true clinical benefits of VEGF inhibition in renal carcinoma. A further question will be whether the status of pVHL influences the response to such therapy. The findings of Yang and coworkers could serve as a platform for the rational integration of antiangiogenic agents into cancer therapy.

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Cochlear Implants

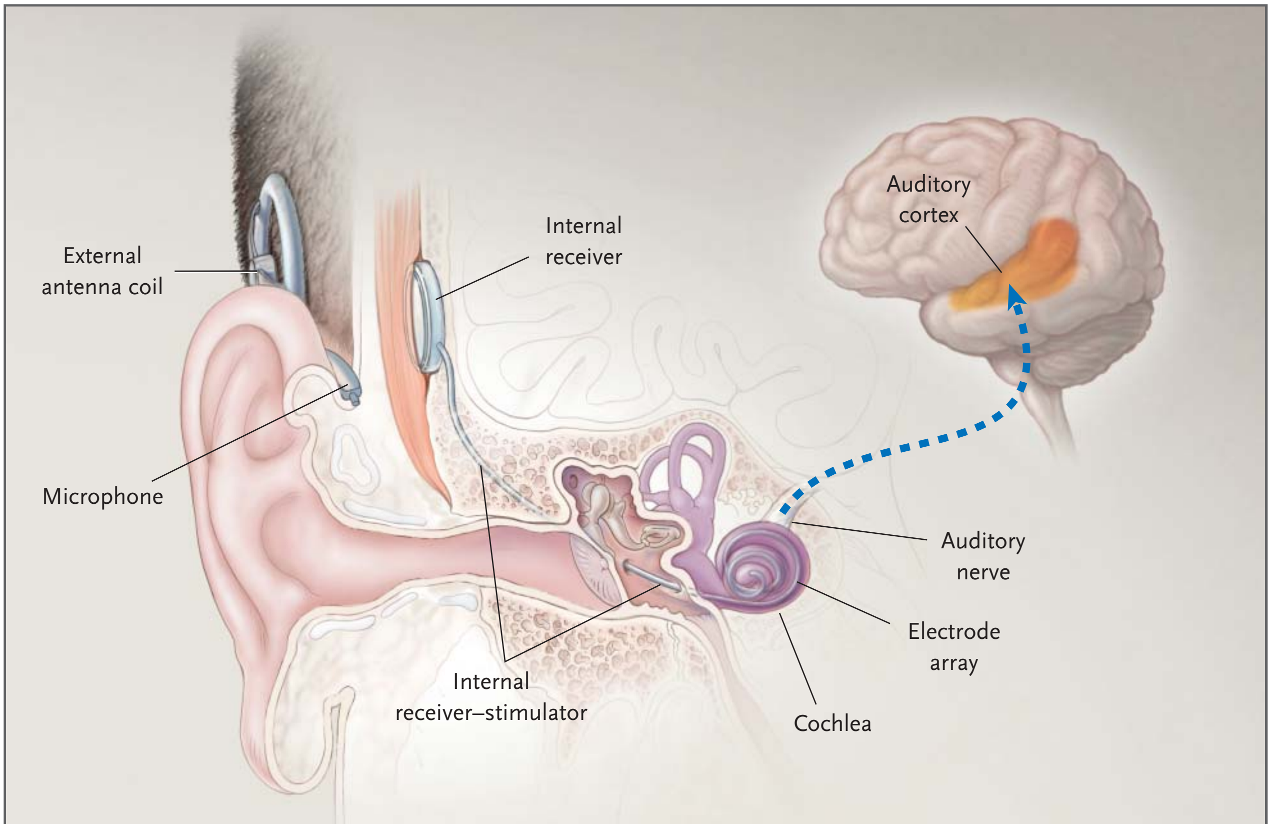
George A. Gates, M.D., and Richard T. Miyamoto, M.D.

Currently, a cochlear implant is the standard treatment for people whose hearing ability is so poor that well-fit hearing aids fail to permit effective oral communication. The implant is a neural stimulator whose electrode array is placed surgically in the lumen of the cochlea, near the auditory nerve. An external microphone picks up speech signals, and the signal processor transforms these signals into digital impulses that a radio-frequency carrier transmits percutaneously into the internal receiver–stimulator and electrode array (see Figure). The auditory cortex is stimulated by the implant, permitting the perception of the digitally processed information as speech.

Cochlear implants represent a life-changing use of technology. With the implant plus lip reading, people with severe-to-profound hearing loss are able to communicate orally at a nearly normal pace with near-normal accuracy, in most cases. The implant does not recreate the sensation of the normal human voice. The sensation it produces varies, and most recipients report that it is high-pitched and mechanical at first. Brain adaptation undoubtedly is responsible for the almost-universal perceptual change over time toward normal speech sensations. The cost of cochlear implants per quality-adjusted life year (approximately $9,000) is favorably low, because there is a great improvement in the quality of life and a moderate total cost (about $40,000 for adults and $60,000 for children, including the device, surgery, and rehabilitation).

Current implant technology is sophisticated, mature, and reliable. Worldwide, about 60,000 implants have been placed during the past 20 years, approximately half of them in adults and half in children. About 1 million people in the United States are potential candidates for cochlear implants, and three companies have received approval to sell the devices. The outcomes among patients who receive various models are similar; there is no reliable method for predicting whether one type of implant would provide better or poorer results than another for any given patient. The use of a device that is familiar to the medical center performing the implantation has advantages in terms of programming and service.

The chief predictor of success is a short duration



Design and Function of the Cochlear Implant.

of hearing loss. Early implantation is preferable in children, so that they may take advantage of the window of opportunity for language learning that begins to narrow after two years of age. For adults, chronologic age is not a factor. Healthy, active octogenarians use cochlear implants to great advantage.

The optimal use of implants requires detailed, individual fitting, auditory rehabilitation and training, and daily practice. For people without language (such as infants), additional special education is required for the development of language. Thus, implantation always carries a substantial commitment to habilitation and rehabilitation. Although the costs of the implant and the surgery are covered by most health insurers, reimbursement for auditory rehabilitation, the key element of success, is often minimal.

People are often unsure whether they should obtain an implant, when it should be placed, and which ear should be used. Recent experience has also aroused concern about the prevention of meningitis.

For most adults and children with severe-to-profound hearing loss, the use of an implant is the only viable choice for effective oral communication. For adults who have been deaf since a prelingual age and who live in a world where sign language is the standard, opting for an implant carries social as well as medical ramifications. Some deaf activists still oppose implantation for cultural reasons, but they are a shrinking group. Indeed, the widespread use of cochlear implants in children has changed the face of deaf education, with early mainstreaming for most. The total costs of implantation and mainstream education are substantially lower than the costs of residential deaf education, and the outcome in terms of language, reading ability, and employability are substantially better for people who receive implants during childhood.

As a rule, the implant should be placed earlier rather than later, particularly in children. Most adults have progressive worsening of auditory function with time; therefore, there is no advantage in waiting. Current guidelines endorse implantation when a person can identify only 50 percent of key words in spoken sentences with a best-fit hearing aid in the poorer ear and 60 percent or less of the key words with such a hearing aid in the better ear. For the deaf prelingual infant, the recommendation to place a cochlear implant is generally based on a lack of progress with well-fit hearing aids and intensive auditory training. Universal screening of the hearing of newborns facilitates early recognition of hearing loss. The current minimal age for the placement of implants recommended by the Food and Drug Administration is one year, but implantation performed even earlier may be advantageous for language development.

Surgeons generally place the implant in the ear that has a functioning auditory nerve. If there is residual hearing in both ears, most centers place the implant in the ear with poorer hearing. If the hearing is the same in both ears, the right side is preferred, because of the right-ear advantage that occurs with age. If a patient has been totally deaf in one ear for years, it may be preferable to place the implant in the better ear. Testing of balance may also help in making this decision, since it would be helpful to avoid using the ear with better balance function.

No one can predict how well the device will work for any person. The question really is how hard the person will work to learn to use the device. For adults who became deaf after having acquired good speech and language and who have been deaf for a short time, the norm is to achieve an ability to understand running speech and some ability to use the telephone. "Hearing" with the implant improves with time and practice.

Complications from cochlear implantation are unusual. Recent reports of postoperative meningitis have called attention to a previously unrecognized risk. In this issue of the *Journal*, Reefhuis et al. (pages 435–445) describe the scope of this problem. Since most cases of meningitis in the study reported by these authors occurred in children with abnormally developed cochleae and in those who received an implant that included a positioner device, it is likely that the mechanism of infection was a direct communication from the middle ear through a damaged or abnormal pathway. Use of the positioner has now been discontinued. Prevention by immunization, meticulous sealing of the cochleostomy site, and urgent treatment of otitis media are recommended. In adults with normal cochleae, the risk of meningitis is very low. However, before implantation, it would be prudent for all patients to receive the appropriate pneumococcal vaccine, and *Haemophilus influenzae* vaccine should be given to unvaccinated children. Vigilant observation is warranted.

The use of bilateral implants has led to small improvements in patients' understanding of speech, particularly in settings where there is background noise, and in sound localization. Hybrid devices that provide both acoustic and electrical stimulation are being investigated for people with profound high-frequency hearing loss. Totally implantable devices are under development.

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Do Bisphosphonates Make Children's Bones Better or Brittle?

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Bisphosphonates such as alendronate (Fosamax, Merck) and pamidronate (Aredia, Ciba–Geigy) are synthetic analogues of inorganic pyrophosphate. The main effect of bisphosphonates, which are deposited on the surface of bone and ingested by osteoclasts during bone turnover, is antiresorptive. They inhibit the mevalonate pathway in osteoclasts, enhancing apoptosis and inhibiting skeleton re-