Paparella: Volume II: Otology and Neuro-Otology

Section 3: Diseases of the Ear

Part 4: Inner Ear

Chapter 47: Metabolic Hearing Loss

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Hearing loss is associated with a systemic metabolic dysfunction in a higher incidence than would be expected from an otherwise comparable population. In some of these types of hearing loss, a defect in the metabolism of the inner ear can be identified; in other types, the mechanism by which the systemic metabolic dysfunction affects the ear is unclear. There are also entities in which a metabolic dysfunction exists in the inner ear without any systemic metabolic dysfunction. In this chapter, an overview of the appropriate mechanisms of both systemic and inner ear metabolism is followed by a discussion of those metabolic disorders that are associated with hearing loss.

There are basic metabolic processes that are almost universal within the cells of the organism and that are essential to maintain both the structures and function of these cells. The living cell has the ability to synthesize large molecules from relatively simple chemical compounds. The cell can likewise break down large molecules into smaller units, and energy may be released by this process. This energy is stored in the high-energy phosphate bonds of adenosine triphosphate (ATP). In animals this energy is produced from the oxidation of fats, carbohydrates, and proteins. Anaerobic metabolism can produce some energy, but it is much less efficient than aerobic metabolism. Metabolism is a complex process with many intermediate stages. This intermediate metabolism is highly integrated, and any one metabolic pathway is interwoven with many other interlocking pathways in a very complex manner. All of these metabolic processes depend on enzymes.

Enzymes are complex proteins with a specific stereochemical structure. Enzymes act as catalysts and decrease the energy of activation required for the various chemical reactions. In order to function, enzymes may require the presence of cofactors such as metals or vitamins. Most enzymatic action is very dependent on such factors as temperature, pH, and the ionic concentrations of the fluid substrate. The presence or absence of any particular enzyme is dependent on the presence or absence of a specific gene. Therefore, metabolic activity can be regulated at many levels, and the coordination of this regulatory function is essential to the normal function of the living cell.

The first level of regulation is at the site of actual chemical reaction. At this site, control depends on such factors as the concentration of the basic chemical reactants, the presence or absence of the appropriate enzyme and its required cofactors, and the pH and temperature.

The next level of regulation is based on feedback inhibition. Many enzymes are inhibited by the final product of their reaction or by products that occur further along the metabolic pathway.

The third level of regulation is via genetic control. As noted, the presence of any particular enzyme depends on the presence of a particular gene. Garrod characterized certain diseases as inborn errors of metabolism. He pointed out that when a certain enzyme is missing, the precursor of the reaction may build up and the end-product may be lacking. Also, a diversion of the metabolic pathway may occur with a side-product of the precursor of the reaction being produced.

The concentration of the active form of the enzyme is dependent on the respective rates of synthesis and degradation of the enzyme, and the rates may be varied by the presence of inducing or repressing agents. Whole sequences of enzymes may be induced or repressed as a group because the genetic information required for their production is coded sequentially on the DNA chain.

In higher, multicellular organisms, metabolic functions are further integrated through the endocrine and nervous systems. Hormones or neural transmitter substances affect the cellular activity by acting to stimulate or inhibit the metabolic activity of the cell membrane, the cellular enzymes, or the genes directly. The first messenger (the hormone or neural transmitter substance) transfers information across the cell membrane by utilizing cyclic adenosine monophosphate (cAMP), the so-called second messenger.

Each individual cell has receptors that respond to particular hormones. The hormone receptors of one type of cell can be different from those of other types of cells, so that the hormone can specifically stimulate or inhibit particular groups of cells. Adenylate cyclase is the enzyme that produces cAMP and inorganic phosphate from ATP in a reaction requiring magnesium and manganese. Adenylate cyclase exists in the cell membrane. A receptor subunit is located on the outside surface of the cell membrane, with a catalytic subunit on the inside surface. The hormone or neurotransmitter reacts with the receptor, and this changes the rate of cAMP formation within the cell. The concentration of cAMP may alter the concentration of specific enzymes or other aspects of the cell's internal metabolism. Exactly how this occurs depends on the particular hormones or neurotransmitters involved and on the particular type of cell.

Inner Ear Metabolism

The inner ear is a metabolically active organ. The function of the cochlea is to transduce mechanical stimuli into electrical impulses. This function requires energy, and this energy is derived from oxidative metabolism. That is to say, oxidative metabolism provides the energy used for the transportation of ions to maintain the electrical potentiators and to provide for the day-to-day maintenance of the cell structure.

Although the cells in the organ of Corti actually transduce the mechanical stimuli into electrical impulses, this organ is not the most metabolically active site within the cochlea. The organ of Corti has sufficient carbohydrate stores and a glycolytic pathway and an intrinsically lower oxygen requirement than the stria vascularis. The stria vascularis is the most metabolically active site in the cochlea. The stria vascularis contains high concentrations of ATPase, which breaks down ATP to provide energy. This enzyme is also found in the spiral ligament and on the surface of the organ of Corti in contact with the endolymph. The enzyme is not present in the hair-cells where they contact cortilymph. ATPase is present on the

endolymphatic side of Reissner's membrane. Reissner's membrane also shows a level of adenylate cyclase. The stria vascularis relies on oxidative metabolism to provide energy to maintain the ion concentrations and the electrical potentials within the inner ear.

Abnormalities in the pathways of oxidative metabolism are uncommon, but there are suggestions that they can be the cause of hearing losses. For example, biotinidase deficiency is associated with hearing loss. Biotinidase-deficient children cannot recycle endogenous biotin and become biotin-deficient. Degradation of their carboxylases probably results in the production of biocytin or larger biotinyl peptides, which in the absence of biotin may alter the metabolic pathways involved in the development and/or function of the auditory system. In a similar fashion, defects associated with the leucine catabolic pathway (which is also involved in biotinidase deficiency) have also been associated with hearing loss.

Fluid and Electrolyte Metabolism

The cochlea, like all other organs, requires a controlled internal environment of electrolyte concentrations. The kidney, under the influence of antidiuretic hormone and aldosterone, controls the concentrations of these electrolytes within the body. The posterior pituitary gland produces antidiuretic hormone in response to changes in osmolarity monitors by hypothalamic receptors. Aldosterone is produced by the adrenal cortex. Patients with alterations in their body sodium concentrations, such as those that may follow major surgery, often complain of a fullness in the ear which resembles the symptoms described by patients with Ménière's disease.

Ménière's Disease

Ménière's disease is associated with endolymphatic hydrops. The cause of this hydrops is unknown; however, it has been suggested that abnormalities of fluid and electrolyte production or absorption in the inner ear are responsible for the hydrops.

The loss of function associated with Ménière's disease tends to stop progressing with time. The pathologic correlate as to why this occurs has not been established, but one explanation might lie in the fact that two types of degenerative changes have been observed in Ménière's disease. These are vacuolation of the sensory cell cytoplasm and cystic degeneration.

There is a possibility that Ménière's disease is due to an autoimmune response to type II collagen. Endolymphatic hydrops has been induced in guinea pigs by immunizing them with native type II collagen, for which the antibody responses were specific. Some patients with Ménière's disease have collagen immunity, and this may play a part in the etiology of the disease. The levels of antibody to type II collagen were higher in the patients with Ménière's disease, whereas the levels of antibodies to type I and type IV collagen were not raised.

Renal Disease

Diseases of the kidney have been associated with hearing loss. It is considered that the disorders of fluid and electrolyte metabolism resulting from the renal disease are the cause

for the hearing loss. The hearing loss in patients on dialysis does not appear to be correlated with the level of uremia or the degree of electrolyte abnormality, but it does correlate somewhat with the number of dialyses. There are often other conditions or complications that may be alternative explanations for all or part of the hearing loss observed in patients with renal disease. These conditions include the use of ototoxic diuretics and ototoxic antibiotics, the presence of infection, diabetes mellitus, hypertension, and arteriosclerosis and the hemodynamic changes associated with renal dialysis and/or transplantation.

In 1927, Alport described a syndrome of chronic nephritis, hematuria, and progressive renal failure in association with hearing loss. This syndrome is transmitted as an autosomal dominant, but the chromosome in which the abnormal gene resides is preferentially selected in association with the X chromosome. There may be an abnormality of a structural gene at a locus governing the composition of basement membrane in the glomerulus, inner ear, and lens capsule. There have been numerous biochemical studies of the glomerular basement membrane.

Males are affected more severely than females. The hearing loss usually begins about age 20, and the audiometric pattern may be "trough-shaped", sloping, in which the high frequencies are affected most, or flat. Severely affected males used to die by age 30 from their renal disease, but now successful transplant surgery and hemodialysis are increasing the longevity of patients with Alport's syndrome.

Histologically there are degeneration of the stria vascularis, a loss of cochlear neurones, atrophy of the spiral ligament, loss of hair-cells, and deposits of basophilic substances in the stria vascularis. Such basophilic deposits, however, are not specific for any particular disease, including Alport's syndrome.

Previously there was some optimism that renal transplantation would improve the hearing in patients with Alport's syndrome; more recent studies have not borne this out.

Other syndromes that involve renal disease are associated with hearing loss. These include renal tubular acidosis, associated with high-tone hearing loss; a syndrome of hypertension, renal failure, steroidogenesis, and hypogenitalism; Charcot-Marie-Tooth syndrome and nephritis; a syndrome of renal disease, hyperprolinuria and ichthyosis; a syndrome of nephritis, urticaria, and amyloidosis; and a syndrome of renal disease, epilepsy, mental retardation, and diabetes.

Oxygen Metabolism

If the inner ear is deprived of oxygen there are orderly sequences in which the cochlear structures are affected, and once oxygen is resupplied these structures recover in the reverse order. In the hypoxic cochlea the oxygen tension falls first in the tunnel of Corti and then along the cochlear duct. The endolymphatic potential falls progressively along the cochlear duct, and a decrease in the endolymphatic potassium-sodium ratio occurs, as does a decrease in the cochlear microphonic potential. The stria vascularis is entirely dependent on oxidative metabolism. The half-life for ATP in the stria vascularis is approximately 1 minute, compared with 30 minutes in the organ of Corti. The stria vascularis is therefore more sensitive to oxygen lack.

Electrophysiologically, the area of auditory function first to be affected by anoxia is the auditory cortex, followed by the inferior colliculus and then the outer hair-cells, as measured by cochlear microphonics. Although the nerve fibers can transmit impulses, spontaneous nerve fiber activity and the response to sound are lost during anoxia. This suggests that anoxia may affect transmission from the hair cell to the first-order neuron. The sensitivity of this hair cell dendrite junction may be a factor in fluctuating hearing loss. There are many processes that may decrease the oxygen supply to the cochlea. Reestablishment of this oxygen supply is the theoretical basis for therapies such as vasodilators for sudden hearing loss. Drugs, hypercholesterolemia, arteriosclerotic vascular disease, hyperlipidemia, hypercoagulability, and inflammation all may result in hypoxia of the cochlea. Aspirin produces a reversible hearing loss, presumably by uncoupling oxidative phosphorylation. Sodium salicylate has been shown to cause vacuolization of the lateral smooth endoplasmic reticulum cisternae in the outer hair-cells, suggesting an osmotic disturbance. It also causes a change in stiffness of stereocilia, suggesting an ionic disturbance within the cells. Rabbits fed a high-cholesterol diet developed arteriosclerosis and hearing loss. This hearing loss appears to be secondary to end-organ ischemia rather than a toxic effect of cholesterol.

Viral and allergic inflammation can affect the cochlea directly by producing cellular damage, and they can also affect the cochlea indirectly by causing hypoxia. The hypoxia is due to such factors as damage to the endothelium and edema, erythrocyte disruption, vasoconstriction, platelet aggregation, and hypercoagulability. Reversing any or all of these factors may improve the oxygenation of the cochlea.

Calcium and Phosphorus Metabolism

A number of bone diseases are associated with hearing loss. These include otosclerosis, osteogenesis imperfecta, Paget's disease, osteopetrosis, cranial dysostosis, craniometaphyseal dysplasia, craniofacial dysostosis, and Treacher-Collins syndrome.

Otosclerosis

Otosclerosis is a disease of the otic capsule, which is transmitted as an autosomal dominant gene with variable penetrance. Otosclerosis is generally associated with fixation of the stapedial footplate and conductive hearing loss. Cochlear otosclerosis may cause sensorineural hearing loss. This sensorineural hearing loss may be due to the presence of cytotoxic enzymes in the perilymph or to shunting of blood away from the membranous labyrinth, with subsequent hypoxia. Otosclerosis may also physically distort the basilar membrane.

Lesions resembling the spongiotic changes of otosclerosis have been produced in rats by immunizing them with type II collagen. However, these lesions were not at the stapediovestibular joint. In these experiments, immunofluorescent deposits were found in the endochondral layer of the otic capsule. Patients with otosclerosis were found to have increased levels of antibodies to type II collagen, whereas they did not have any increase in the levels of antibodies to type I or IV collagen. This suggests that an immunity to collagen may play some part in the etiology of otosclerosis. It has also been suggested that otosclerosis is associated with vitamin D deficiency.

Osteogenesis Imperfecta

Type I, or nonlethal, osteogenesis imperfecta is characterized by bone fractures during childhood, blue sclerae, and hearing loss. The hearing loss is due to an otosclerosis-like lesion fixing the footplate and can be treated by stapedectomy. The disease is transmitted by an autosomal dominant gene. The gene is a nonfunctioning allele for pro alpha-1(I) chains of type I procollagen. The patient therefore synthesize pro alpha-2(I) chains of type I procollagen, and these are incorporated into trimers of type I procollagen. However, how this type of collagen defect is responsible for the stapedial fixation is not yet clear. The endosteal bone of the cochlear capsule is affected.

Osteopetrosis

In osteopetrosis, which is transmitted by a dominant gene, the bone is abnormally hard and brittle. The hearing loss associated with this disease is a mixed conductive and sensorineural type. There are overgrowth of bone at the foramina and structural abnormalities in the inner ear, and these changes seem to be the cause of the sensorineural hearing loss. Severe cases of osteopetrosis, which previously were fatal, can now be treated with a bone marrow transplants, but the outcome so far as hearing is concerned in such patients is not yet known.

Abnormalities of Parathyroid Hormone or Vitamin D Metabolism

Hearing loss can occur in osteitis fibrosa cystica secondary to development of a cyst adjacent to the inner ear. It is assumed that the hearing loss is due to pressure, and the hearing may improve once the parathyroid abnormality is treated. Vitamin D deficiency can cause a sensorineural hearing loss, and in at least one reported case, treatment with vitamin D improved the patient's hearing. Hyperphosphatasia and hypophosphatasia have been associated with hearing loss, and recently it has been recognized that sensorineural hearing loss is a common complication of X-linked hypophosphatemic osteomalacia.

Metals

Lead. Lead poisoning may occur from ingesting lead or from inhaling lead-containing fumes. Lead is very toxic to neural tissue. In the central nervous system, lead causes intense edema with destruction of brain cells and neuroglia. In the peripheral nerves, lead affects the axon. Neuropathies including wrist drop, blindness, and deafness occur. These neuropathies may be irreversible despite treatment with edetate.

Iron. While hearing loss has not been reported with hemochromatosis, there is some evidence that the basis for the hearing loss associated with thalassemia may be iron overload.

Bilirubin Metabolism

In neonates with significant jaundice, a deposit of golden-brown pigment can occur in the basal ganglia. This condition is known as kernicterus. Bilirubin is a breakdown product of the heme ring of hemoglobin. The lipid-soluble unconjugated bilirubin is conjugated in the liver to produce a water-soluble product that is excreted in the bile. A neonate may develop

kernicterus because of several factors. First, the placenta no longer clears bilirubin from the neonate's circulation, and the neonatal liver lacks the enzyme glucuronyl transferase, which is necessary for conjugation. Mother's milk may contain some substances that inhibit conjugation of bilirubin, and, finally, there are no bacteria in the gut to convert bilirubin to urobilin.

Albumin binds bilirubin in the blood, with the average albumin-binding capacity for bilirubin being about 25 mg/100 cu cm (with 3 g albumin/100 cu cm). This corresponds well with the fact that a level of 20 mg/100 cu cm of bilirubin is usually an indication for an exchange transfusion.

An Rh-negative mother can become isoimmunized to her Rh-positive fetus. The most common Rh factor involved is D. The mother produces antibodies that hemolyze the fetal blood, causing the severe jaundice of erythroblastosis fetalis. Other Rh factors as well as incompatibilities can also cause jaundice.

The neonate's bilirubin-binding capacity can be lowered by low albumin, cold, anoxia, acidosis, infection, salicylates, and sulfonamides. If the bilirubin-binding capacity is lowered to below 20 mg bilirubin/100 cu cm, kernicterus can occur.

Pregnant women who are at risk for Rh incompatibility should be monitored for isoimmunization. If isoimmunization occurs, then during the pregnancy, amniocentesis can be performed and, if necessary, an intrauterine transfusion can be performed. In a neonate, the bilirubin levels can be lowered by phototherapy with ultraviolet light or by an exchange transfusion.

The hearing loss of kernicterus appears physiologically to be associated with a cochlear lesion. Degenerative lesions have been demonstrated in cochlear nuclei and central auditory pathways of severely jaundiced neonates. The pigment in the cochlear nuclei is deposited tonotopically so as to cause a high-tone hearing loss. No pathologic changes have been demonstrated in the temporal bone. However, the auditory brain stem responses of such infants suggest that some cochlear pathology exists.

Carbohydrate Metabolism

Diabetes Mellitus

There is some disagreement about whether diabetes mellitus can cause hearing loss. Some studies have not demonstrated any changes in pure-tone or speech audiometry. On the other hand, in patients with diabetic retinopathy, standard audiometry may not reveal any defect, whereas filtered speech task will reveal a decrease in hearing acuity. Diabetes mellitus has been claimed to cause a fluctuating hearing loss.

The mechanisms by which diabetes mellitus may produce hearing loss include small vessel disease causing hypoxia of the inner ear, primary diabetic neuropathy, neuropathy due to involvement of vasa nervorum, or alterations in inner ear glucose levels.

Changes in the small vessels have been noted on histologic examination of temporal bones taken from diabetic patients. A deposition of PAS-positive material occurs in the capillary walls of the stria vascularis, with aneurysmal dilatation of the capillaries and a decreased number of cells in the spiral ganglion.

The primary diabetic neuropathy may be due to the accumulation of sorbitol within the nerve tissue. The secondary neuropathy is due to a decrease in the blood flow of the vasa nervorum. The neurons show a thickened basement membrane of the Schwann cells, segments of demyelinization, and changes in the biochemistry of the lipids. Some of the changes are reversible, and clinically the patient may improve with metabolic control.

The inner ear utilizes glucose to produce energy, and changes int he glucose concentration in the inner ear may alter the hearing. It has been shown experimentally that the endolymphatic potential of animals may be altered by altering the systemic insulin concentration.

Other syndromes exist in which diabetes mellitus is associated with hearing loss. The Didmoad syndrome consists of diabetes insipidus, insulin-dependent juvenile diabetes mellitus, and progressive high-tone hearing loss. Alström's syndrome is characterized by retinitis pigmentosa, diabetes mellitus, obesity, and hearing loss. Herman's syndrome consists of hereditary nephritis, mental retardation, epilepsy, diabetes mellitus, and hearing loss.

Adrenocortical Insufficiency

Adrenocortical insufficiency may be associated with the symptom of Ménière's disease, presumably due to a defect in the regulation of sodium. Other patients with adrenocortical insufficiency complain of an increased sensitivity to sound and have decreased pure-tone thresholds, decreased discrimination, and a loss of sound localization but to not have recruitment. These patients also have smell and taste problems. The lesion may be central, and perhaps the alteration in the time constants of neural transmission may be the cause of the decreased discrimination. Prednisone appears to help this condition.

In adrenoleukodystrophy, there are a primary failure of adrenal gland function and degeneration of the neural white matter. The disease is progressive, and there is no effective treatment. The disease is characterized by gait disturbances, dysarthria, dysphasia, visual loss, and a hearing loss with preservation of the caloric response of the vestibular system.

Protein Metabolism

Enzymes are proteins, and so it can be said that any hearing loss due to an enzyme defect is due to abnormal protein metabolism. Of course, most enzyme defects present as a combination of systemic findings (ie, a syndrome). One group of diseases is due to an abnormality of a protein that normally transports substances, such as a lack of ceruloplasmin, which transports copper, in Wilson's disease or a deficiency in albumin, which binds bilirubin, in kernicterus.

Another group of diseases is associated with pigmentary changes and hearing loss, which may represent changes in tyrosine and phenylalanine metabolism.

Waardenburg's syndrome is characterized by hypertelorism, a flat nasal root, and confluent eyebrows. There are two types, classified by the presence or absence of dystopia canthorum. About half of the patients have a white forelock and heterochromia iridis. Sensorineural hearing loss occurs in approximately 50 per cent of type I patients and 20 per cent of type II patients. Half the patients with hearing loss have vestibular disturbances. Waardenburg's syndrome is transmitted by an autosomal dominant gene. The temporal bone histology shows absence or degeneration of the organ of Corti and the stria vascularis, atrophy of the spiral ganglion, and a paucity of nerve fibers.

Certain other forms of hearing loss are associated with abnormal pigmentation. Hearing loss may be associated with albinism and with the leopard syndrome.

Hearing loss in animals is also associated with pigmentary changes. Studies of such animals give us models for Michel's and Mondini's deformities, and also for the investigation of profound deafness of hereditary origin. Scheibe's deafness is common in animals such as pallid mice, white cats, and Dalmatian dogs. There is evidence that the hearing loss is not due to melanin lack per se.

Homocystinuria is due to a recessive gene. Methionine metabolism is abnormal because of a deficiency of the enzyme cystathione synthase. Some patients can be helped by vitamin B therapy and a diet low in methionine.

Hypercoagulability

If the blood supply of the inner ear is cut off owing to thrombosis, sudden deafness may result. The hearing loss may be of slower onset, resulting from inner ear hypoxia. The diagnosis of hypercoagulability is made by using the prothrombin consumption time. Occasionally anticoagulants may restore the hearing. In polycythemia, phlebotomy may reverse the hearing loss.

Lipid and Lipoprotein Metabolism

Lipid Storage Disease

Lipid storage disease includes a group of diseases in which specific enzymes involved in the hydroxylation of the various products of catabolism of sphingolipids make up the cell membranes and occur in high concentrations in tuberous tissue. Hearing loss has been observed in Gaucher's disease, Niemann-Pick disease, Krabbe's disease, metachromatic leukodystrophy, Fabry's disease, Tay-Sachs disease, and generalized gangliosidosis. Tay-Sachs disease occurs almost exclusively in Ashkenazy Jews. A screening test for the genetic trait is currently available to pregnant women who are at risk for bearing affected children. Fabry's disease is due to an X-linked recessive gene. There is a lack of alpha-galactosidase, and neutral glycosphingolipids are deposited in body tissues.

Phytanic Acid (Refsum's Syndrome)

Phytanic acid is a fatty acid found in the gut. Patients with Refsum's syndrome lack the enzyme that normally converts phytanic acid to pristanic acid. This syndrome appears to

be due to a recessive gene. The clinical characteristics of the syndrome include retinitis pigmentosa, cerebellar ataxia, ichthyosis, sensorineural hearing loss, and a hypertrophic neuropathy affecting sensory and motor nerves. Patients have improved on a diet low in phytol and phytanic acid. Fibroblast cultures can be used to detect heterozygous carriers of the gene. A prenatal diagnosis can be made by amniocentesis. The temporal bone histology in patients with Refsum's syndrome shows collapse of Reissner's membrane, atrophy of the organ of Corti, strial degeneration, and loss of cells in the spiral ganglion.

Lipoprotein Metabolism

A lack of lipoproteins in the rare condition of beta-lipoproteinemia causes ataxia, acanthosis, and hearing loss. Demyelinization, which occurs both in the central nervous system and in peripheral nerves, probably is the basis of the hearing loss.

There are a variety of hyperlipoproteinaemias. Types IIA, IIB, IV, and V are due to a dominant gene, whereas types I and III are due to a recessive gene. Types II and IV are the types most commonly associated with hearing loss. How the hearing loss is related to the high serum lipid concentration is not known, but end-organ hypoxia or partial vascular obstruction may play a part. Once the type of hyperlipoproteinemia has been identified, the treatment is mainly by diet; however, cholestyramine, clofibrate, nicotinic acid, and dextro-thyroxine can also lower serum lipid levels.

Mucopolysaccharide Metabolism

A group of syndromes in which abnormal mucopolysaccharide metabolism is associated with hearing loss includes Hurler's, Hunter's, Morquio's, and Scheie's syndromes.

In Hurler's syndrome, which is inherited through an autosomal dominant gene, the temporal bones contain mesenchyme-like tissue and are incompletely formed, suggesting an arrest in fetal development of the temporal bone. A temporal bone from an adult with Hurler's syndrome also had no malleoincudal joint, no normal cells in the organ of Corti, and a stria vascularis that had disintegrated, although the spiral ganglion was fairly normal.

In Hunter's syndrome, which is due to an X-linked gene, the deafness is mixed. Mesenchyme-like cells with foamy, PAS-positive cytoplasm (gargoyle cells) are found in the middle ear and mastoid, and similar PAS-positive material is found in the spiral and vestibular ganglia and the small blood vessels below the stria vascularis.

In Morquio's syndrome, which, like Hunter's syndrome, is due to an inborn error of mucopolysaccharide metabolism, hemorrhage occurs in the middle ear and there is widespread damage to collagen.

The mannosidoses are a related group of syndromes. In this group of diseases the metabolism of mannose is abnormal owing to the lack of enzyme alpha-manosidase.

Thyroid Metabolism

Thyroid hormone incorporates iodine into thyronine. Thyroid hormone is necessary for normal growth, development, and maturation of the organism. Thyroid hormone functions by uncoupling oxidative phosphorylation on ATP by acting on the intermediaries in the Krebs citric acid cycle. Normal metabolism does not take place when thyroid hormone is not present. The effects of the lack of thyroid hormone are well documented by endocrinologists, but the reason why a lack of thyroid hormone is associated with hearing loss is not well understood.

Endemic cretinism is due to a severe iodine lack over several generations. The affected individuals have a goiter and are mentally retarded. A progressive mixed hearing loss occurs in over 50 per cent of these patients. Thyroid hormone can reverse the mental retardation but does not help the hearing loss. Endemic cretinism is a nongenetic but congenital type of thyroid deficiency in humans. It has been associated with deformities of the malleus and incus, incomplete ossification of the stapes, distortions of the round and oval windows, poorly developed mastoid processes, thickened middle ear mucosa, and hyperostoses of the promontory, and even with occasional closure of the round window.

In experimental animals, induced congenital hypothyroidism has been associated with a decreased number of hair-cells and spiral ganglion cells, strial degeneration, and acidophilic precipitates in the cochlear duct.

Other types of nongenetic acquired hypothyroidism are associated with hearing loss. These include sporadic athyroid cretinism and juvenile and adult acquired hypothyroidism. In sporadic athyroid cretinism, there is abnormal development of the embryonic thyroid; as maternal thyroid hormone crosses the placenta, the infant develops normally, but after birth the infant becomes hypothyroid. Juvenile hypothyroidism results from infections such as measles or pertussis. In a study of 45 children with congenital thyroid gland agenesis, hypogenesis, or dyshormonogenesis, one-fifth has sensorineural hearing loss. Adult hypothyroidism may follow drug treatment, surgery, or irradiation. It may also result from infections or dietary lack of iodine. Some cases are idiopathic; 25 to 50 per cent of these patients develop a hearing loss that is occasionally reversible with thyroid hormone treatment, but this did not occur in patients over 60 years of age. The level of hearing loss correlates somewhat with the severity of the hypothyroidism.

The ears of experimental animals made hypothyroid showed a variety of histologic changes. These included thickening of the tympanic membrane and of the middle ear mucosa, eustachian tube obstruction, and ossicular anomalies. In the inner ear there were a loss of hair-cells, changes in the spiral ganglion cells, and a general regeneration of the organ of Corti, including the tectorial membrane. There also was a loss of the cochlear potentials, and the animals developed a hearing loss within about 120 days; investigators still do not understand the exact pathophysiology of the hearing loss.

Pendred's syndrome represents a genetic, congenital type of thyroid dysfunction. The disease is inherited through an autosomal recessive gene. In 1836, Pendred described a case of congenital hearing loss, sporadic goiter, and slow development in an otherwise normal patient. What has come to be known as Pendred's syndrome is due to a lack of the enzyme

peroxidase, which interferes with the organification of iodine. The bilateral sensorineural hearing loss is another manifestation of the gene and is usually moderate, with a slope down toward the high frequencies on the audiogram. Patients with Pendred's syndrome are euthyroid, and a positive perchlorate or thiocyanate flush of the goiter is diagnostic. Thyroid hormone does not help the hearing loss. Temporal bone studies have shown hyperostosis of the round window and Mondini-like deformity of the inner ear in some cases.

A group of diseases are associated with genetic abnormalities of the enzymes involved in thyroid hormone production. Because maternal thyroid hormone crosses the placenta, the intrauterine development of the infant is normal and manifestations of hypothyroidism do not occur until the postpartum period. The incidence of the association of such types of hypothyroidism with hearing loss is not known, but it is thought that the hearing loss is probably due to the lack of thyroid rather separate expression of the gene.

Autoimmune Sensorineural Hearing Loss

The condition that was described by McCabe in 1979 presents as a progressive sensorineural hearing loss over weeks or months, which usually is bilateral but may be asymmetric. The hearing loss is reversible with steroid therapy; cyclophosphamide may be used as an adjunct to the steroids. Patients should be screened by assays including sedimentation rate, rheumatic factor, antinuclear antibody titer, and quantitative immunoglobulin determination. If any two of these are elevated and the history is suggestive, a leukocyte migration inhibition test should be done. If this test is not available, a trial of treatment should be begun. In a study of six patients with steroid-responsive sensorineural hearing loss, four had raised levels of circulating immune complexes.

In about half the patients with Wegener's granulomatosis, hearing will improve once the disease is treated. The vessels of the endolymphatic sac are involved in Wegener's granulomatosis, whereas the vessels of the rest of the inner ear are spared. This mechanism may be the basis of other forms of autoimmune sensorineural deafness.

Miscellaneous Metabolic Defects

There are many reports of sensorineural hearing loss associated with metabolic defects in the same patient; however, many of these reports described only one or two patients. It will take time to evaluate the true significance of such reports.

Prevention and Treatment of Metabolic Hearing Losses

Some forms of metabolic hearing loss can be treated. Thyroid hormone may prevent the development of the hearing loss in hypothyroid patients and may improve the hearing in some affected patients. Similarly, vitamin D may improve hearing in patients deficient in this vitamin. Steroids and cyclophosphamide will improve the hearing of patients with autoimmune hearing loss. Sodium fluoride has been used to prevent the sensorineural hearing loss of otosclerosis, and diphosphonates may act in a similar fashion. Diphosphonamide has been claimed to improve hearing in a small number of patients with Paget's disease. Hopefully, the use of medications such as calcitonin may prevent the progress of Paget's disease and so prevent the hearing loss.

Phlebotomy can improve hearing in patients with polycythemia. Phototherapy and exchange transfusions, including intrauterine exchange transfusions, can prevent the development of kernicterus in infants with Rh incompatibility. The use of RhoGAM can prevent the isoimmunization of the Rh-negative mother of an Rh-positive child.

Dietary restrictions can prevent the development of hearing loss in such conditions as Refsum's disease. The effects of a high-cholesterol diet may be a factor in developing a hearing loss. Rosen suspected that one factor in the excellent preservation of hearing in the members of the Mabaan tribe of the Sudan may have been their diet.

Tissue transplantation may have a role in the treatment of hearing losses. Early reports of improved hearing in patients with Alport's syndrome after transplantation have been supplanted by more recent reports that are much less optimistic about improvement in the hearing of such patients. Bone marrow transplants have been used to treat osteopetrosis and Hurler's syndrome.

Many forms of metabolic hearing loss are genetically determined. Prenatal testing for the heterozygous state of many such genetic diseases exist. WIth the development of such techniques as restriction endonucleases, monoclonal antibodies, and high-performance liquid chromatography, more such tests for the presence of particular genes are becoming available. Tests to identify sickle cell carriers or Tay-Sachs disease carriers have been available for some time. Newer techniques have enabled the identification of carriers of Huntington's disease and phenylketonuria. Also, more accurate tests for sickle cell disease and thalassemia are now available. These techniques may involve sampling fetal tissue by amniocentesis or chorionic villi sampling. Currently, an explosion of the applications of such technology is under way.

The application of such prenatal probes to diseases carried as dominant genes or to high-risk groups is obvious. Unfortunately, many genetic hearing losses are transmitted as recessive genes, and this makes the application of such prenatal forms of diagnosis much more haphazard. For example, such diagnosis of phenylketonuria is practical only in families in which one affected child has already been born.

The ultimate treatment of genetic types of hearing loss would be the insertion of a replacement for the defective gene into the cells of an affected individual. It is possible to insert viral genes into experimental animals. However, attempts to transfer genetic material in humans have been unsuccessful. Obviously, there are many ethical problems that must be considered, along with the technologic problems.

Although the clinical stage of ongoing studies with gene therapy is drawing nearer, such statements as "therapy may be only a step away" are overly optimistic. For example, many of the hemoglobinopathies are understood down to the last nucleotide and yet remain essentially noncurable.

Another rather pessimistic report is one about a calf which was a bovine "freemartin" chimera with manosidosis. This calf died from the neurologic manifestations of the disease. This report opens questions about the possibility of using grafted normal cells to treat such diseases.