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Etiology of otosclerosis

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THE ETIOLOGY OF OTOSCLEROSIS

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INTRODUCTION

In writing this summary of the literature on the etiology of otosclerosis, it was the hope that a general knowledge of the theories advanced up to the present might be obtained. That by this means the progress in this field might be evaluated and that some of the problems presenting themselves in the treatment of otosclerotic patients made easier.

Otosclerosis always has been a social problem and sooner or later every physician is confronted with the responsibility of advising some patient suffering from the disease.

Is the disease inherited? Is treatment therefore of no avail and must we look forward to unfavorable prognosis in all cases? Should a patient with otosclerosis marry and have children? Would pregnancy incite otosclerosis in the mother? Or if she has otosclerosis would it contribute to the advancement of the disease? To what extent are we able to prevent otosclerosis by eliminating possible etiological factors?

Moreover, otosclerosis is characterized by certain psychic changes, notable mental depression and an attempt to limit all social intercourse. Are these changes the

result of the condition of being deaf, or are the changes just as much a part of otosclerosis as the changes in the labyrinthine capsule? Questions like the above can only be answered by studying the etiology of the condition.

The work here begins with the earliest work done on the subject and as nearly as possible each reference is added more in its place in the development of the literature than the real subject matter it contains.

The work of the "Committee on Otosclerosis" of the American Otological Society has been used constantly for material. The manner of presenting the subject under Hereditary Causes, Congenital Causes, Local Causes, and General Causes was suggested by this same work.

HEREDITY AS AN ETIOLOGICAL FACTOR

The history of otosclerosis up to the time of Toynbee, in 1851, (9) is a collection of fragmentary bits of anatomy and physiology, some correct and some incorrect, but all leading to a basic knowledge essential to later studies. Toynbee examined about twelve hundred cases of diseased ears anatomically, and became interested in stapes ankylosis, which he attributed to a "rheumatoid arthritis." It is also interesting in that there was found a family history of deafness in ma ny of his cases.

Von Troeltsch, in 186?, (1) states that chronic catarrh of the ear, under which term he includes sclerosis and stapes ankylosis, often has a hereditary basis.

In 1910, Hammerschlag (1) referring to the genealogy discussed in his previous contribution showed the association of hereditary degenerative deafness and otosclerosis in the same family. He maintained that otosclerosis and hereditary degenerative deafmutism are different manifestations of the same hereditary process, on the following grounds: (1) The degenerative-atrophic process in the nerve and the nerve terminals found in congenital deafness are probably entirely the same as

those found in otosclerosis. (2) The characteristic bone changes of otosclerosis in the labyrinthine capsule are found also in some cases of congenital deafness. (3) There are families in which hereditary deafness and otosclerosis are associated. He also pointed out elsewhere that progressive labyrinthine deafness is also based on a congenital disposition and is regarded by many otologists as definitely hereditary. In a case of progressive labyrinthine deafness reported by Manasse, an isolated new-form focus of spongy bone was found in the internal auditory meatus in addition to the typical pathological changes in the nerve. The findings indicate that progressive labyrinthine deafness is a primary degeneration atrophy of the acoustic nerve which may not be manifest until late in life, but in individuals with a constitutional inferior auditory organ is manifest in the early life period. It seems possible to state that hereditary degenerative deafness, progressive labyrinthine hardness of hearing and otosclerosis represent merely different manifestations of a genetically uniform disease.

Korner (1) is of the opinion that Siebenmann's interpretation of otosclerosis as an abnormal postembryonic process of growth definitely favors the theory of its hereditary transmissibility. Any process of growth,

and degenerative stigmata. The family histories showed that not only otosclerosis was present in the family in some cases, but also diseases known to develop on the basis of constitutional inferiority (diabetes, premature arteriosclerosis, chlorosis, etc.). According to present knowledge only the tendency to otosclerosis can be regarded as inherited. In a case presented, the family history would support the theory of Hammerschlag that hereditary degenerative deafness, progressive labyrinthine deafness and otosclerosis are only different forms of a single genetic disease.

In 1901 Gray (1), in a review of the various theories of the etiology of deafness, concludes that otosclerosis is a definite pathological change in the bony capsule of the labyrinth, bilaterally symmetrical, making its appearance very gradually and occurring in individuals who may be in the best of health. The majority of individuals never have otosclerosis no matter how badly their general health may be affected nor from what cause, or whether they suffer from local disease of the ear such as suppuration or catarrh or not. The logical conclusion to be drawn is that the basic cause of otosclerosis is to be found in the organ of hearing itself and also that this condition exists in the organ of hearing of certain individuals only. From this point of view oto-

are born; it follows from Mendel's law that the number of transmittors has no tendency to diminish in the successive generations. Consanguineous marriages may result in the union of two transmittors with resultant appearance of the disease in the offspring.

Abnormal heredities, according to Bauer and Stein (4), in 1925, originate through so-called germ variation or idiokinesis, namely, through alteration of one or more genes, under the influence of some harmful factor acting unpon the parental organism. In their article on endocrine affections of the auditory organ (1926), they point out that a positively established fact in the etiology of otosclerosis, as well as progressive labyrinthine hardness of hearing, is not some anomaly in one or several endocrinic glands, but rather the hereditary constitutional disposition, transmissible through the germ plasm. It is readily understood that such a constitutional disposition can be inherited also, when the most careful investigations of the family in so far as practicable, fail to reveal an analogous affection.

Drury (1926), (1), maintains that the law of inheritance explains the character of otosclerosis as an inherited abnormal process of development. A suggestive etiologic factor in otosclerosis is that it begins about the time of puberty. During this period the cells that are

on their way toward specialization may, if conditions become altered, especially in a predisposed person, de-differentiate, becoming embryonal again and then starting off on a new line of differentiation. The cases he presents illustrate "the general thesis of the etiological background of otosclerosis." In both there is the constitutional tendency as indicated by the family history, and in both there are evidences of a disturbance of general metabolism, which the author believes is a factor in the determination of otosclerosis.

It is rahter remarkable that on investigator apparently sees only cases with dominant heredity, while another sees only recessive cases, so that it cannot at once be recognized which heredity is to be considered as the rule and which as the exception. It is a remarkable fact that Albrecht has seen for the most part dominant cases, whereas Bauer and Stein say mostly recessive cases. Perhaps this is explained by the different hereditary dispositions to otosclerosis having a different geographical or ethnic distribution. Further investigations on a larger material must aim at the solution of all these questions, after overcoming the many still-existing difficulties of human heredity, and perhaps may furnich a simpler possibility of interpretation of the still apparently complicated relations.

lies in the sex chromosome, and a factor A, which lies in one of the autosomes.

In the human species the male has only one sex chromosome while the female has two.

On the basis of the foregoing hypothesis, the authors conclude:

The female zygote has the same chance as the male of getting an Y-chromosome from the egg. About half of the female otosclerotics have received their affected Y-chromosome from the egg; the other half have received an affected Y-chromosome from the sperm. Hence, we should expect twice as many zygotes carrying an affected Y-chromosome in the females as in the males--and this agrees closely with observation.

Otosclerosis in identical twins was recently described by Shambaugh (1935)(10). This comparatively rare occurrence has been observed a total of five times. The author concludes that the large proportion of otosclerotics show signs of prior inflammatory episodes in the middle ear and nasal sinuses; and this would appear to be in conformity with the contention of Fowler.

The underlying cause of otosclerosis--as propounded by Guggenheim (1931-32-33-34)(4)(7)--is mesenchymal and embryonic, or supervenes soon after the fetal period. He originates and, in his book (1935), maintains the

regression theory of otosclerosis was presented to the otologic world. This theoretical structure is erected upon a very insecure foundation. It is based upon the finding of bony lesions similar to those found in otosclerosis in the otic capsule of a fetus of seven months. A parallel is drawn between the finding of a closure of a preformed oval window in the herring and other fishes and the ankylosis of the stapes and the obliteration of the round window in cases of otosclerosis. In the cases of the herring and the sturgeon the obliteration of the preformed window is accomplished with normal bone and cartilage. The otosclerotic lesion is distinctly pathologic. It is contended that in otosclerosis there is a reversion on the part of the human labyrinthine capsule to the fish stage."

According to the experimental findings of Levy in 1934 (4), who fed white mice with calcium fluoride,-- these findings are opposed to the regression theory of Guggenheim.

In the discussion of the startling theory propounded by Guggenheim in his lecture before the New York Academy of Medicine (1932), it was pointed out by J. Gordon Wilson (4), with respect to the fissula as an alleged vestigial organ, corresponding to a structure found in certain fishes, that no trace of the fissula

CONGENITAL CONDITIONS IN THE LABYRINTHINE CAPSULE

In 1879, Wendt (1) noted that the anatomical condition of the niches of the windows of the labyrinth as well as the distance between the tegmen and the head of the malleus and the body of the incus, and the dimensions of the tympanic cavity in general facilitated the occurrence of abnormal adhesions. An unusual depth of the niche of the oval window appears especially to favor the origin of adhesions of the stapes to the adjacent bony walls.

A distinction between chronic catarrhal otitis media and sclerotic otitis was made by Gradenigo in 1887 (1). The later, he stated, is not uncommonly hereditary. It has a particularly constant pathological feature lesions of the labyrinthine windows and especially ankylosis of the stapes. These characteristics of sclerotic otitis indicate that it is a pathological condition of embryonic congenital origin closely related to the morphology of the ear. In his embryological studies of the ear in the mammals and man, Gradenigo has found that the stapes is derived from the fusion of two distinct morphology elements, the stapedial ring being derived from the second branchial arch and the stapedial lamina or

foot-plate from the labyrinthine capsule. The chief, practically the only, lesions of sclerotic otitis involve the vestibular wall of the tympanic cavity and the stapes, namely, parts which show a complex embryonic development; the usual site of the lesion is, therefore, determined by a morphological factor. The author does not claim that stapedio-vestibular ankylosis must also be regarded as a pthognomonic lesion of sclerotic otitis, but he emphasizes that in view of its complex embryonic formation this articulation represents a point of diminished resistance in certain pathological processes of the ear.

The reason why the labyrinthine capsule shows a tendency to transformation of the compact bone into loose spongiosa (as stated by Siebenmann in 1899) (1) is probably accounted for by the fact that the normal labyrinthine capsule throughout life is exceptionally rich in remnants of primary cartilage. This cartilage lies in smaller or larger foci in the vicinity of the labyrinthine spaces. These foci occur most frequently in the region of the posterior wall of the oval window and in the basal end of the upper wall of the cochlea, also in the lower cochlear wall, i.e., exactly in those areas that represent the sites of predilection for the spongiosa formation.

Professor G. Bruhl of Berlin (5) summarizes his beliefs on the subject of otosclerosis with five points:

1. Clinical otosclerosis is identical with osseous ankylosis of the stapes.

2. For proper investigation of otosclerosis more cases of ankylosis of the stapes diagnosed in vivo should be studied before many conclusions are drawn on the subject.

3. Otosclerosis is a constitutionally conditioned, hereditary affection, a kind of degeneration or atavism, but not a disease. Therefore, it is idle to look for its cause as for the cause of a disease.

4. Not all departure from the normal labyrinthine bone structure should be classed as otosclerosis orincipient otosclerosis.

5. The true pathologic bony form leading to ankylosis of the stapes consists of a spongelike, new-formed bone which starts from the spaces surrounding the periosteal blood vessels in front of the vestibular window. By mechanical (orchemical) irritation there is a disturbance of the old bone by resorption and later a replacement by new bone. The new bone is formed in excess and is therefore to be recognized as tumorlike new-formed bone. Between the most anterior portion of the tensor tympani tendon and the anterior border of the annular

ligament lies a portion of the cochlear wall, dubbed by Bruhl the "ostosclerotic corner." In the adult, in contrast to the embryo, the anterior portion of the annular ligament is broader than the posterior portion.

The irritation of the movement at this point, where the foot plate moves farthest and the pull of the tensor tympani in the opposite direction, Bruhl believes tobe factors in the production of otosclerosis. This is especially the case in individuals hereditarily predisposed to the hyperostoses which often form in this region. The stress and strain of the pulling and the irritation of the hyperostoses together are, in his opinion, most important in the causation of otosclerosis.

Otto Mayer (6), in his article entitled "Die Enstehung der Spontanen frakturen der Labyrinth kapsel und ihre Bedeutung fur die Otosklerose," as reviewed by Guggenheim, first outlines the theory of G. Bruhl as to the cause of otosclerosis. Bruhl believes that a mechanical irritation of the area anterior to the oval window results from (1) constant movement of the annular ligament, and (2) the contractions of the tensor tympani muscle. Then follows Mayer's argument against this theory. Against: (1) "If it were true that the new bone formation is the result of the mechanical irritation from the annular ligament, one would expect that the new bone

formation would begin in the cartilage layer. I possess four temporal bones with beginning new bone formation on the anterior border of the oval window, in which the cartilage layer is perfectly normal, the new bone being anterior to it and impossible of irritation from the pull of the annular ligament." Proof against point (2): "The contraction of the tensor tympani muscle cannot irritate the point of predilection, as the muscle has no relation to this area. Just anterior to the oval window, the muscle lies in a canal lined with thick, firm connective tissue in which the muscle and tendon move freely. The tendon passes around the processus cochleariformis, which should be the irritated point, and the pocessus cochleariformis shows no otosclerotic changes nor does the bone to which it is attached. Also, Bruhl's theory could not explain otosclerosis in the region of the oval window, internal auditory meatur and region of the canals."

Concerning Bruhl's theory, which Mayer attacks, Guggenheim states that one might say that even though the annular ligament does not impinge directly upon the bone in which otosclerosis begins, it may well be that there is a constant though slight irritation transmitted through the cartilage, which irritation may be related to otosclerosis. Also in the case of the tensor tympani pull, there

may be a transmitted irritation. Bruhl claims only that these constant irritations may be sufficient to start otosclerotic bone changes in susceptible individuals. Neither Mayer nor Bruhl has thrown any light upon that individual peculiarity which makes the development of otosclerosis possible.

In 1914, Manasse (1) reported that in a study of the petrous bones from two hundred cases he found peculia r characteristic cartilage islands in the bony capsule of the labyrinth. They consist of hyaline cellular cartilage, with at most a few isolated very fine fibers; bits of calcium, sometimes larger masses of calcium, may be imbedded in the ground substance of this cartilage. Closely relaged, but without any genetic transition into these cartilage foci, there are usually found small foci of immature (although not very young) bone, non-osteoid, and containing fat-marrow spaces. In view of the fact that the author found these foci from the age of infancy on, he is inclined to interpret them as congenital arrest malformations; the peculiar bone, which was not demonstrable in very young subjects, is perhaps referable to a pathologically incomplete ossification.

Certain analogies with osteitis chronica metaplastica of the labyrinthine capsule (otosclerosis) are

considered by the author as interesting: (1) The seat of both affections is in the labyrinthine capsule. (2) Both have an identical seat of predilection. (3) The metaplastic foci appear as a rule bilaterally and also symmetrically. (4) Newly developed bone is found in the metaplastic foci as well as in the cartilage islands. (5) In both affections, there exists at the same time an atrophy of the membranous labyrinth. As, in one of the author's cases of otosclerosis, the cartilage foci were found besides spongification of the stapes plate on one side, close relations between the two affections are regarded by him as very probable, although the foci described in the foregoing are not as yet to be considered as the substratum of the congenital predisposition to otosclerosis.

In 1917, Manasse (1) noted the site of predilection for the pathological changes of osteitis chronica metaplastica (otosclerosis), i.e., the anterior margin of the oval window, is the same site where anomalies in the structure of the bony capsule of the labyrinth are most frequently found, and that they are most undoubtedly congenital. These anomalies are of two types: inclusions of cartilage and inclusion of fat marrow. The author has not yet been able to find a definite connection between the cartilage and fat-marrow foci and osteitis

found hyaline cartilage between the tensor tympani tendon and the oval window. The cartilage foci are situated in the bone of the labyrinthine capsule, partly surrounded by interglobular spaces, in which are numerous blood vessels surrounded by a bony sheath (or mantle). These cartilage islands in the labyrinthine capsule are found at the site which is the site of predilection for the pathological changes of otosclerosis. The conclusion that these cartilage remnants represent the arrested development of variable etiology and offer a point of diminished resistance to the otosclerotic process or perhaps even a preliminary stage of this process seems to be justified. This conclusion supplies a satisfactory explanation for the symmetry and typical localization of the otosclerotic foci, for the hereditary character of the disease, and also for the occasional association of otosclerosis with congenital syphilis, cretinism and other constitutional anomalies which are known to be associated with retarded ossification.

Mayer (1) has contributed at various times to the literature. In 1904 he maintained his theory that the otosclerotic foci are to be interpreted as proliferations that develop from embryonic tissue malformations, belonging to the group of hyperplasias that originate

hand, more or less marked malformations of the ear are found in otosclerosis. It is a very valuable fact that this malformation of the cochlear spindle according to Siebenmann is found especially in the hereditary form of congenital deafmutism, because numerous investigations have shown that otosclerosis likewise represents a decidedly hereditary disease.

On the basis of his findings Mayer (1) concludes that: Not only the histological character of the foci, but also the multiplicity, the typical localization and symmetry, the existence of minute islands of atypical tissue at the sites of origin of the foci, furthermore also the simultaneous occurrence of malformations in the internal ear and in other regions of the auditory organ, as well as the hyperplasia of the entire petrous bone, the clinically established association with congenital signs of degeneration, and finally the heredity, are in favor of the assumption advocated by the author, that the foci are to be interpreted as tumor-like hyperplassias. Only on the basis of this assumption is the entire clinical and anatomical picture rendered intelligible. No other theory is capable of placing otosclerosis on the basis of general pathology, for while all the other attempts at explanation postulate an entirely new unknown pathological process, the author's theory

is linked with known processes in other systems of the organism. On the other hand, we do not know why in one case large otosclerotic foci develop from embryonic osteoblastic tissue, while in other cases the growth fails to occur or advances only to a certain extent and then stops.

Otto Mayer (5) in recent years has found very striking, spontaneous and presumably nonsymptomatic fractures in the temporal bones of several cases of Paget's disease. Mayer finds his fractures very often in the promontory, near the anterior border of the oval window, and feels that from more careful study of the stresses we shall find this the weakest part of the bony capsule, and the part of the bone most subject to powerful mechanical influences. He does not say that otosclerosis is the callus of a healed fracture; rather he believes that a continuous strain on primitive bone in hereditarily predisposed individuals accounts for the growth of a mature bone, otosclerotic bone. The fractures merely indicate the regions where stress and strain take place.

Mayer's explanation (4) as to the cause of fissures or fractures in the labyrinth capsule is not accepted by L eiri (1929), who refers the production of these fissures essentially to: (1) The pulsation of the

carotid artery against the labyrinth. (2) The movements of the stapes footplate in the oval window. (3) The tension of the membrane in the basal coil. In addition to these purely mechanical factors, also other forms of irritation act upon the labyrinth capsule.

Eschweiler (1933)(4) as regards fissures in the labyrinth capsule, states that the tissue content of the fissures as well as their localization and the absnece of any reaction indicate their correct interpretation as artifacts. Lange likewise observed the fissures described by Mayer in his temporal bone specimens and, like Eschweiler, he interprets them as artifacts. The observations of Keleman (1933), do not permit him to draw conclusions as to the relation of such fissures to otosclerosis. Also Loebell and Nack (1933), do not discuss the significance of these fissures or their eventual relation to otosclerosis.

Hans Brunner, in an article entitled "ueber Soaktbuldung in der knochernen Innenohykapsil," which is reviewed by L.K. Guggenheim of St. Louis, explains the fissures as follows: (1) They may occur around vessels or bundles of connective tissue in the bone. (2) They may occur in the sense of O. Mayer (spontaneous fractures). Brunner doubts that the fissures are really spontaneous fractures due to some mechanical disturbance

of the temporal bone: no blood, pigment or any reaction processes are noted. Brunner thinks the fissures are either canals for vessles or are dehiscences. He cannot agree that a callous formation from these fissures is related to otosclerosis: first, because the fissures are most common in the canal region, where otosclerosis is seldom seen, and rarely in the oval window region, where otosclerosis is most common. Again, the most common site of traumatic fissure is the tegmen tympani, where otosclerosis has not been found.

The criticism on Mayer's spontaneous fractures as stated by Guggenheim is--that there seems no longer any doubt that Mayer's fractures are really fissures occurring during life and not artifacts as some have claimed. The presence of fibrous tissue in the fissures, he states, would seem to settle that question. That these fissures should occur in elderly people at the site of predilection for otosclerosis is certainly of significance. He says that many men are under the impression that Mayer has claimed that these spontaneous fractures are the cause of otosclerosis. Mayer has offered no such theory. He believes that in young bone, the strain, which in the old bone results in fracture, sets up sufficient disturbance, in predisposed individuals, to cause certain bone changes which ultimately result in the histologic

iron chloride. The result is a disturbance in the bone which Wittmaack believes to be identical with that found in human otosclerosis.

Wittmaack's (1930)(4) venous stasis theory on the genesis of otosclerosis is based upon the explanation of the local absorption process as a bone absorption which is elicited through a venous stasis with considerable rise of the venous blood pressure. Under the pathologic conditions on which the evolution of the otosclerotic process is based, however, the blood stream within the venous tracts here concerned evidently follows the opposite direction and is forced in a retrograde course into the emerging vein of the area of special predilection. He emphasizes that the otosclerosis problem can never be entirely understood, let alone solved, by looking exclusively at the otosclerotic absorption process itself. It is only by way of the peculiarities of the focus and a careful study of its vicinity, with special attention to the venous drainage path, that the connection will be clearly shown between the otosclerotic focus and the characteristic reversal of the blood current within the venous tracts, which are to be regarded as the actual cause of the diseased focus (13).

Wittmaack himself raises the pertinent question as to the cause back of the venous stasis. There may well

be a multiplicity of causes bringing about this condition. The venous stasis theory does not conflict with the established hereditary predisposition to otosclerosis in a certain percentage of cases. A special inherited proclivity to premature dysfunction of the vascular walls may possibly be a powerful factor in the production of venous stasis.

An investigation of O. Mayer's "spontaneous fractures" by Wittmaack, has led him to entirely different conclusions (1933) (7) as to their origin; he not only denies the existence of true fractures--many are undoubtedly aftifacts--but he emphasizes that even granting the existence of genuine fractures, no light would thereby be shed on the otosclerosis problem, because the debatable changes do not occur at the points of predilection for otosclerosis.

Guggenheim states points in criticism of Wittmaack's work. He states that no doubt Wittmaack has produced experimentally his findings, but we must keep in mind that the structure of the hen's capsule is different from the human; that the experimentally produced condition is always generalized as to the capsule, whereas otosclerosis occurs at certain sites of predilection; that except for the presence in otosclerosis of certain vessels gorged with blood corpuscles, there is no proof

for the statement that venous stasis exists in this condition. Guggenheim states that it is common knowledge that early cases of otosclerosis show large vessels which contract in later stages; that these enlarged vessels may be physiologically due to increased bone activity, and that therefore Wittmaack has failed to prove that there exists venous stasis in otosclerosis; that the two types of capsules in hen and man are not comparable, and finally that Wittmaack himself has finally realized that, stasis or no stasis, there is an hereditary factor in otosclerosis which he has failed to uncover.

Gray (1934)(6) has had the opportunity of examining Wittmaack's preparations and he is of the opinion that the newly formed bone produced as a result of these experiments is in no way different from those which is found in otosclerosis. Furthermore, he agrees with Wittmaack that these changes in the bone are the result of stagnation of the blood in the smaller blood vessels. Now it appears to Gray that the stagnation of blood in the bone at this particular region is not difficult of explanation if it be admitted that the essential defect in otosclerosis is to be found in the vasomotor mechanism governing the nutrition of the organ of hearing.

Weber (1930)(19) approaches the problem of otosclerosis from the standpoint of bone pathology. He expresses

festations in the human otic capsule form the subject of an extensive study of Nager and Meyer (1932) (4), who on the basis of their findings maintain that otosclerosis belongs to the group of osteodystrophies. The experience that similar changes have been produced in bones by various experimental procedures suggests that the bone changes observed in the osteodystrophies, including otosclerosis, are not due to any specific cause, but represent a general reaction of bone tissue to various metabolic disturbances.

On the basis of various considerations, Boederlein (1908-1933) (4) is inclined to assume that the process of change in the bone is similar to that in rickets or osteomalacia, so that a general cause is presumably responsible in all these affections. Certain differences of the bone changes in otosclerosis are readily accounted for by the peculiar structure of the labyrinth bone as compared to all other bones of the body.

Demineralization of the bones is charged as the causative factor in otosclerosis by Pallard (1930) (4), who considers the ear disease as of essentially the same nature as other osteodystrophies, while restricted to the bony capsule of the labyrinth. Not an actual deficiency of phosphorus and calcium is responsible, but rather a deficient fixation of these two elements, which

are excreted without having been properly utilized by the tissues. Functional disturbances of the endocrinic glandular system are the recognized cause of such demineralization processes and he assumes that the thyroid is probably primarily active in this regard through hyperfunction in otosclerosis.

The new bone formation in otosclerosis, according to O. Mayer (1923-1939) (4), is a resorptive new formation of a primitive reticular bone; this process takes place at certain definite sites in the labyrinth capsule, namely, at the windows and occurs in the form of foci or bands, which surrounds these sites in the form of rings. Because of its peculiar situation and its tendency to hyperplasia, the new bone formation has been described as a tumor-like hyperplasia. Mechanical strains are held responsible for this new bone formation. The osteogenesis of otosclerosis is of callous type and is referred by Mayer and others to a mechanical functional origin. Its objective is to build resistant bone at the points exposed to the greatest strain. In his article on otosclerosis (1917), the focal affection was interpreted by Mayer as a special form of tumor-like hyperplasia and was grouped under the heading of the so-called hamartomas.

Greifenstein (1935) (4) raised the important question whether the histologic picture of otosclerosis oc-

curs solely and exclusively in the labyrinthi capsule, or whether the same or a similar picture is to be found under certain pathologic conditions also outside of the labyrinth capsule? Should this be the case and should moreover the reasons be known for the origin of such otosclerotic pictures outside of the labyrinth capsule, valuable indications would thereby undoubtedly be furnished for the origin of otosclerosis itself. This question was approached by Greifenstein, on the basis of extensive studies of the bone tissue by means of polarized light. In his opinion, an otosclerotic focus, judging from its biologic behavior, may originate anywhere in the presence of vascular marrow spaces with specific germinal tissue.

INFLUENCE OF LOCAL CONDITIONS

Toynbee (1), in his description of speciments in which stapes ankylosis was found, notes as a rule that the mucous membrane of the tympanic cavity is thickened and the tympanic membrane often opaque and somewhat thickened. He states that the mucous membrane of the tympanum may be subject to chronic inflammation, complicated or not by rheumatism, and if this is neglected it is liable to terminate in a rigid state of the membrane. It is this change in the tympanic cavity, the author believes, that results in the various stages of stapes ankylosis.

It was pointed out by von Troeltsch (1), in 1859, that the relationship was close between the tympanic mucosa and the adjacent portions of the petrous bone which would naturally lead to secondary bone affections developing from disease of the tympanic mucosa. He also notes that the blood supply and vascularization of these parts were also connected so that any nutritional disturbances in the tympanic mucosa would react upon the closely connected and subadjacent periosteum and the bone itself.

It was stated by Bertuch (1868)(1) that a frequent cause of ankylosis of the stapes is middle-ear catarrh.

In catarrh of the tympanic cavity the entire mucous surface often shows condensation and thickening and the mucous covering of the stapes and the annular ligament is also involved. In severe cases, a deposit of calcium salts takes place in the thickened mucosa, so that the tympanic membrane and the stapes become rigid and immovable. Another pathological change referable to catarrh of the tympanic cavity is the formation of adhesive bands between the crura of the stapes and other parts of the tympanic cavity, especially the adjacent wall of the niche of the oval window. Processes of calcification and ossification also take place in these bands with resulting complete fixation of the stapes.

Schwartz, Wendt, Magnus, and Moos are other earlier contributors who thought that a chronic catarrhal condition was responsible for stapes.

In 1888, Gradenigo (1) maintained that while the persistence of embryonic gelatinous tissue is an important factor in sclerotic otitis some other factors are undoubtedly necessary for the manifestation of the disease pathologically and clinically. One of these factors, found in the majority of cases, is disease in the nasal mucosa which extends to the tubotympanic mucosa.

In 1889, Cholewa (1) states that, in his opinion, otitic sclerosis is the result of a chronic catarrh of the

Eustachian tubes and tympanic mucosa, as well as a neurosis of the fifth and the sympathetic nerves. Either of these conditions may suffice to produce the symptom complex of sclerosis, but both factors combined usually form the basis of the disease, and together induce the secondary affection of the labyrinth.

Scheibe (1) notes that he has also found circumscribed osteitis of the labyrinthine capsule in two cases of chronic middle-ear suppuration, but he is unable to accept the view that inflammation of the middle-ear mucosa is a frequent cause of such pathological changes in the labyrinthine capsule, as in such cases the tympanic membrane is frequently entirely normal.

Steinbrugge (1893)(1) states that permanent changes in the tympanic mucosa may result from frequent recurrence of catarrhal inflammation, as well as in consequence of chronic hyperemia. In some cases the mucosa is considerably thickened by increase of its connective tissue and also shows evidence of venous hyperemia. Changes in the connective tissue result in the development of the condition known as "sclerosis," which manifests itself especially in the deeper periosteal layers. Various sclerotic changes may also develop in an insidious fashion without preceding inflammatory processes. In such cases the tympanic mucosa is usually not involved, or only to a slight

degree. But there is often congestion of the vessels in the handle of the malleus and, still more important, a chronic hyperemia of the mucosa of the labyrinthine wall. The malleus incus joint may become ankylosed; the niche of the oval window, the window margins, and the annular ligament of the stapes foot plate are usually involved in the sclerotic process. Hereditary predisposition is probably an etiological factor in middle-ear sclerosis. Chronic hyperemia of the mucosa and any factor that tends to produce such a chronic hyperemia are regarded by the author as important etiological factors in this insidious type of middle-ear sclerosis.

A definite distinction was made by Heiman (1898)(1) between catarrhal middle-ear disease and middle-ear sclerosis. In his opinion, the latter never develops from the former but represents an entirely different process from the first; the pathological changes in sclerosis are from the first of a degenerative character without a preliminary stage of swelling and hypertrophy of the mucosa and exudation. While the catarrhal form is caused mostly by local factors, the sclerotic form, the author believes, develops almost entirely as a result of general constitutional factors.

Grunert (1903-1904)(1) states the theory that otosclerosis is a sequel to middle-ear inflammation has been

undermined by the fact that the nucleus of the disease consists of very definitely circumscribed pathological foci extending deeply into the petrous bone and not in immediate contact with the middle-ear mucosa. In many cases of otosclerosis moreover careful macroscopical examination has failed to reveal any signs of a previous middle-ear inflammation. In some cases however a preceding otitis media may have been a causative factor in eliciting the characteristic bone disease in the presence of an inherited predisposition.

Bryant (1) in 1908 applied the term otosclerosis to all middle-ear sclerosis; the characteristic changes in the labyrinthine capsule he regards as the labyrinthine extension of the same process in the form of hyperostosis and rarefying osteitis. He prefers the term chronic interstitial otitis to indicate this general pathological process.

The author's (1) clinical observations and laboratory studies have led him to conclude that the pathology of this condition is dependent upon vascular disturbances affecting the blood supply of the tympanic cavity and walls with resultant trophic changes. This disturbance of blood supply may be general or may be confined to one or more of three regions: the drum membrane, the major ossicles, the stapes and labyrinthine walls. The trophic

changes caused by altered blood supply in the middle ear are identical with changes due to similar causes elsewhere in the body--congestion, vascular proliferation, infiltration, interstitial inflammation, hyperplasia, contraction, compression of blood vessels, anemia, degeneration, calcification, vascular osteitis or osteoporosis, and hyperostosis.

While the author believes that the usual primary cause of vascular osteitis of the labyrinthine capsule is alteration of the blood supply of the lining mucoperiosteum of the inner wall of the tympanic cavity, he says that it is natural that this condition may be hereditary since it depends on nervous instability and morphological irregularities, "qualities which are hereditary to a degree."

A review of the literature on the pathological anatomy and etiology of otosclerosis was presented by Bryant in 1913 (1). He also presented his own views on the etiology on the basis of this review and his own clinical and pathological studies. He claims that otosclerosis is a dystrophic and not an atrophic condition of bone, and can be well described by the term "osteodystrophic petrosa." The causes of otosclerosis are manifold in character, but important among them are trophic changes that are caused by toxic influences originating in the naso-pharynx.

From his clinical observations, Dench (1911)(1) is not ready to accept the theory that labyrinthine changes characteristic of otosclerosis are never secondary to middle-ear involvement. In quite a large proportion of cases, he believes the labyrinthine changes are secondary to pathological changes in the tympanic cavity, as is indicated by the fact that the first bony changes characteristic of otosclerosis take place in the outer wall of the labyrinth, i.e., the middle ear in the region of the oval window.

A study of the pathological characteristics of otosclerosis by Mayer (1911)(1) convinced him that this focal disease of the bone is due to local circulatory disturbances in the terminal branches of the nutrient arteries of the petrous bone.

The deficient local blood supply thus responsible for the pathological changes of otosclerosis may be due to vasomotor disturbances or to organic changes in the blood vessels, which may result from general conditions or from inflammation of the middle ear which may cause sclerosis of the local blood vessels. This would explain the relation found by some investigators between middle-ear inflammations and otosclerosis.

Clinical studies of otosclerosis by Gradenigo (1) in 1912 led him to the conclusion that tuberculosis was us-

ually present in the families of otosclerotic patients, often in an attenuated form, although definite evidence of tuberculosis is rarely found in otosclerotic patients themselves. This tuberculous diathesis, however, leads to diminished resistance of the upper air passages, as illustrated by the frequency of adenoids. The author distinguishes three types of adenoids with reference to their relation to the ear:

(1) Adenoids in which the hypertrophy of the pharyngeal tonsil has merely a local action on the lower air passages, without a demonstrable harmful effect of any kind upon the ear. (2) Adenoids in which the nasopharyngeal changes involved the tympanum and the middle ear, giving rise to dry or purulent inflammations of the middle ear, without extension to the labyrinthine windows and the internal ear. (3) Adenoids in which the lesions of the middle ear have more or less tendency to extend to the labyrinthine windows and the labyrinth, with the characteristic changes of otosclerosis.

According to this interpretation, the changes of the mucosa of the upper air passages and the middle ear, in the first years of life determine the establishment of the characteristic bony lesions of otosclerosis later on, under the influence of an attenuated tuberculous infection. Remnants of adenoids have been repeatedly shown

clinically, in adult patients with typical otosclerosis. The frequency of evident signs of adenoidism in otosclerotic patients, and the close relation which it is often possible to establish between ordinary catarrhal chronic otitis and otitis media purulent on the one hand, and otosclerosis on the other, render it probable that the lesions of the bony capsule should be considered as secondary to lesions of the middle ear.

Raoult (1912)(1) notes that he has found neuritis of the peripheral nerves and of the eighth pair, and atrophy of the muscles of the ear in otosclerosis. He is of the opinion that in otosclerosis there is usually a neuritis of the sensory otitic plexus of motor branches, and of the terminations of the auditory nerve, and especially of the vasomotor fibers. Neuritis of the sensory and trophic nerves results in an ischemia of the tympanic membrane and subsequently in periosteal and osseous lesion, fibrous and calcareous degeneration, and all the trophic changes characteristic of otosclerosis. On the other hand the neuritis of the motor nerves immobilizes the muscles of accomodation which results in ankylosis of the ossicles, ankylosis of the stapes in the oval window, and secondarily in the diminution of the circulation with the resulting deficient nutrition of the organ of hearing, and thus the trophic changes mentioned above.

Fraser (1914)(1), in a paper read before the Section of Otology, Rhinology and Laryngology of the British Medical Association, reviewed the various theories of the etiology of otosclerosis. He favored the view that the disease was due to a chronic local infection in the mucoperiosteum of the tympanum in the region of the anterior margin of the oval window and showed lantern slides to prove that it might follow otitis media. The author believes that a chronic infective process may invade the mucoperiosteum of the inner tympanic wall, infect the marrow spaces of the lamellar bone, and finally invade the lymph or marrow space described. When once this has been opened up the chronic infective process may spread around the cochlea between the lamellar and cartilage bone and may progress as far as the internal auditory meatus. This theory meets the objection raised by Politzer, that otosclerosis cannot be secondary to an infection of the tympanic mucosa, because the otosclerotic changes have been found in the region of the internal meatus where there is no mucous membrane connected with the middle-ear spaces.

In discussing the relation of past attacks of otitis media to otosclerosis in 1923 (1), Fraser believes that there is too great a tendency to attribute otosclerosis to one cause alone, and he maintains that an attack

of otitis media may be compared to the "match" or "cigarette end" that lights the fire. The hereditary tendency and the female sex correspond to the "inflammatory material." Any weakening of nerve influences and disorders of the ductless glands that preside over the processes of bone formation and repair may be likened to "a want of water with which to extinguish the fire."

On the basis of his clinical studies, Metzianu (1916-1917)(1), claims that otosclerosis begins with a catarrh of the Eustachian tubes and the middle ear. This form of catarrhal otitis, the end result of which is otosclerosis, is observed in persons who had adenoids in childhood. In order to avoid the development of this form of otitis, adenoids should always be removed in childhood.

Gray (1917)(1) notes a number of cases in which the development of otosclerosis was influenced by local conditions in the middle ear, Eustachian tubes or nasal passages; these conditions may be of the nature of acute or chronic inflammations. On the other hadn, he states that such local conditions are not present in every case and are not an essential factor in the etiology of otosclerosis.

On the basis of his pathological studies of otosclerosis, Wittmaack (1910)(1)(5) concludes that the pathological changes are caused primarily by a venous stasis originating in the venous sinuses near the labyrinthine capsule.

This results in compensatory development of vicarious vascular channels in the bony capsule, which are the starting-point of the characteristic bony changes. His experimentations prove it. The result of these experimental studies is that by means of congestion of the venous sinuses which pass in a special bone channel along the semicircular canals, it is actually possible to produce bone changes in the labyrinthine capsule which even in the fine details of the anatomical process resemble the bone changes occurring in otosclerosis.

In cases studied pathologically by Eckert (1922)(1), he concluded that they resembled very closely the experimental lesions produced by Wittmaack. On this basis Eckert concludes that the pathological changes in otosclerosis are produced by venous stasis and congestion acting upon the bone of the labyrinthine capsule preformed in cartilage.

In 1923, Kamio (1) reported that in attempting to repeat Wittmaack's experiments on chickens by producing stasis in the venous sinuses around the semicircular canals, he came to the conclusion that the operations attempted by Wittmaack do not produce venous stasis in the entire labyrinthine capsule. He finds that the labyrinthine capsule of fowls has an entirely different structure from the human labyrinthine capsule, and that such

port to Wittmaack's theory.

McAuliffe (1927)(1) suggests that strain on the hearing function under the modern conditions of life may favor the development of otosclerosis.

Gray in 1928 (1)(6) maintains the theory suggested in his book on otosclerosis, that the disease is a degenerative process involving the organ as a whole, and is due to an inherent defect in the neurones concerned in the function of hearing.

The essential causative factor in otosclerosis is defined by Gray in 1934 (4)(6) as a slowly progressive failure in the function of the vasomotor reflex of the organ of hearing as a whole. The vasomotor system, which governs the blood supply to the auditory organ, from the external meatus to the cerebral arteries, begins to fail before this time; consequently all the tissues concerned in the function of hearing lose their blood supply to a certain extent. The structures of the organ are not sufficiently nourished to function adequately. Fibrous tissue in the region of the oval window is a degenerative process, with no inflammatory activity, and is due to the deprivation of the extra blood supply to the bone where it is subjected to stress by the movements of the stapes in response to sound vibrations.

The hereditary transmission of a lessened resis-

tance of the autonomous and sympathetic nervous system was pointed out by Bryant (1913) as the responsible factor in otosclerotic heredity.

Disturbances of the circulation, vasomotor disturbances, are credited by Gottlieb (1932) (4) with etiologic importance in otosclerosis. He deems it possible that the heredity of the disease depends upon the hereditary differences in the circulation of the labyrinth capsule.

In a summary of the bibliographic material in the field of otolaryngology of recent years, Dickie (3) quotes Harris as saying that in a study of many cases of progressive deafness no history of suppuration could be elicited. Harris concluded that too much stress has been laid on focal infection.

INFLUENCE OF GENERAL CONDITIONS

Modern genetics looks on genes as the internal directors of development. Rarely does each gene work independently of other genes that are engaged primarily in directing the development of other organs. Always the course of development of the individual and the directing influence of its different genes are modifiable by change of the environment. It is obvious that otosclerosis is not an exception to this rule.

Toynbee (1) again in 1857 advanced the theory that stapes ankylosis was a form of "rheumatic gout" or rheumatic arthritis of the stapedio-vestibular joint. He pointed out that there is a distinct joint between the circumference of the base of the stapes and the inner surface of the fenestra ovalis; and that this stapedio-vestibular joint is decidedly subject to rheumatic gout resulting in various degrees of deafness. The disease, properly called rheumatic gout, affects both fibrous and vesicular structures involved by rheumatic arthritis. Toynbee found that patients with rheumatic gout of the stapedio-vestibular articulation usually showed the uric-acid diathesis; they frequently, but not invariably, had had an attack of rheumatism, gout, or rheumatic gout.

Erhard (1858) (1), who accepted Toynbee's findings in regard to stapes ankylosis as an important cause of deafness, stated that in true bony ankylosis of the stapes, the patients were usually unable to determine the exact time of onset of the condition, or to state any definite cause. Erhard noted, however, that this form of stapes anlylosis was more common in women than in men, and that women who had had children usually noted a distinct decrease in hearing after each pregnancy. He also noted that the great majority of patients showing this type of deafness had resided near the seashore and that the advance of the pathological process was apparently favored by sea-bathing and by exposure to cold.

Other pathogenic factors can be recognized in the majority of cases although Gradenigo (1887) (1) regards anomalies of embryonic development as the essential predisposing cause of sclerotic otitis. In women, he found that the disease often manifests itself or is seriously aggravated during pregnancy and the puerperium, so that each childbirth is followed by definite diminution of hearing. In both sexes, conditions are usually found that indicate abnormal vascular irritability. A number of Gradenigo's patients with sclerotic otitis were examined by Giovanni in regard to the vascular system; a

more or less exaggerated vascular irritability was found in these cases. Gradenigo has noted also that the subjective noises and deafness of sclerotic otitis are increased by all causes favoring congestion in the head.

In 1894, Gradenigo (1) stated that he had recently studied a new series of cases of typical sclerotic otitis, which had developed on the basis of hereditary syphilis. This sclerosis must be regarded as an attenuated form of the typical ear disease of late hereditary syphilis.

Heiman (1898) (1) distinguishes between catarrhal and sclerotic otitis, but states that the same causes may produce either form. He finds, however, that the causes of catarrhal otitis are more often local, those of sclerotic otitis more often general. Heredity is an important factor in sclerotic otitis. Pregnancy is also an important etiological factor, especially if profuse hemorrhage occurs in labor. Among other conditions that may be etiological factors in sclerotic otitis, the author names anemia and chlorosis, chronic rheumatic and gout, leucemia, diabetes and syphilis, overexertion and abuse of alcohol.

It was found by Helot (1) that in pregnant women hearing in some cases is temporarily diminished during

their pregnancy, but returns to normal after delivery. These cases should not be confused with those cases of middle-ear sclerosis in which a permenent diminution of hearing results from pregnancy. In these cases the ear symptoms are most marked after the termination of the pregnancy; in some cases there is diminution of hearing prior to the pregnancy and hearing becomes worse after pregnancy. In other cases, hearing is normal before pregnancy.

The author (1) is of the opinion that sclerosis of the middle ear following pregnancy is due to the fact that during pregnancy there is congestion of the Eustachian tube and the middle ear that is sufficiently prolonged to cause changes in the structure of the mucosa, with proliferation of the connective tissue which becomes fibrotic, and which results in compression of the nerve fibers producing a trophic lesion terminating in sclerosis of the tympanic cavity. Pregnancy is undoubtedly but a secondary cause of the sclerosis in women predisposed to it.

Dickie (1903) (1) concluded from his clinical study of otosclerosis that it is one form of a manifestation of a fault in metabolism, a uric-acid toxemia due to the retention of this metabolic product in the system, a toxemia which attacks the individual "in his most vulnerable point, the labyrinth." In individuals developing oto-

sclerosis, the labyrinth is susceptible to action of the uric acid, either through congenital or inherited factors, or through various acquired conditions, chief among which is the adhesive or non-exudative form of middle-ear disease.

In a brief note commenting on Dickie's article, Downer (1903) (1) expressed the opinion that in all cases of otosclerosis or any other chronic disease of the ear, the patient will be found to have been "a quinine devotee." He is convinced that if quinine could be forever lost to the world, fifty per cent of all chronic diseases of the inner ear would not occur. Quinine, he claims, produces intense congestion of a long-lasting type and the resultant low-grade inflammation is progressive.

From his study of otosclerosis, and especially from a comparison of the findings in sclerosis with those in acute and chronic purulent middle-ear inflammation, Haberman (1903) (1) has become more and more convinced that this disease of the bony labyrinthine capsule must be a very specific type of disease, and he is inclined to regard syphilis as the cause of it.

Denker (1904) (1) is of the opinion that heredity is an essential etiological factor in otosclerosis, and that this may also account for the higher incidence of the disease in the female sex in that the injurious embryonic

influences act especially upon this sex. Pregnancy and the puerperium undoubtedly play an important role in the causation and development of otosclerosis as many women refer the onset of their deafness or its aggravation to the time of pregnancy. Other constitutional conditions and general diseases also enter into consideration, but the author is unable to accept Habermann's view that syphilis is an important etiological factor.

While Gray (1906) (1) is of the opinion that local circulatory changes are a primary factor in producing the pathological changes in otosclerosis, he finds that certain general conditions favor the development of otosclerosis. Pregnancy may be a factor by causing changes in the blood. Of all the general diseases that favor the onset of otosclerosis he has found anemia to be the most important; anemia as well as other general conditions, he believes, favors the stagnation of the blood in the capillaries or the coagulation of the blood in the capillaries or smaller arterioles.

Cornet (1908) (1) notes that of nineteen cases of otosclerosis, he was able to make a complete examination of eighteen cases. Of these eighteen cases, eight were elderly patients with arteriosclerosis or high blood pressure. Of the remaining cases of true otosclerosis, one showed renal insufficiency; one renal insufficiency and

alcoholism; one hepatic insufficiency; two cases showed dyspepsia with gastrointestinal atony; four showed gastrointestinal disturbances of various types with toxemia; and one case had had repeated pregnancies in addition to a constant gastrointestinal toxemia.

While it is impossible to establish proof experimentally that chronic toxemia, especially of gastrointestinal origin, is a cause of otosclerosis, there are certain characteristics of otosclerosis that support this hypothesis: (1) Its insidious development in young subjects in whom chronic toxemias are often latent. (2) Its hereditary character, for the toxemias are also hereditary and probably act upon an auditory organ rendered vulnerable by hereditary conditions. (3) Its frequent development at the time of pregnancy, which results in the special modifications of metabolism. This hypothesis is also in agreement with the known pathological anatomy of otosclerosis as an involvement of the bony labyrinthine capsule, as other bone diseases are also considered as metabolic or nutritional disease, such as rickets and osteoarthritis. The effect of pregnancy with its special disturbances of metabolism further supports this conclusion.

That otosclerosis represents not one but several pathological conditions is the opinion of Harris (1908) (1). In most cases there seems to be a preceding middle-

ear catarrh, and it is possible that the same causes tend to produce both. Many of his cases showed a repeated history of colds. The cause of these colds, the author believes, is not to be found alone or chiefly in the nose; the cause varies in different cases, but the author believes that in many instances it is the condition described by Haig as lithemia or collemia, in which a state of autointoxication exists due to retention of certain products of excretion in the blood. This condition accounts for many cases of throat difficulty, and he is convinced that a similar cause frequently operates to set up or aggravate trouble in the ear. Bacteria also act in causing chronic inflammatory changes as well as more acute suppurative conditions. Other constitutional diseases such as tuberculosis, arteriosclerosis, syphilis, and trophoneurotic conditions, the author believes, do not have a direct causal relation to otosclerosis, but may be regarded as predisposing causes, as rendering every organ of the body more liable to disease. The incidence of the disease is higher in the female sex, indicating that a highly organized nervous system is an important predisposing factor.

That otosclerosis is not catarrhal in origin nor is it the result of inflammation in the ordinary acceptance of the term, nor does it originate in the middle-

ear is expressed by Tweedie (1908) (1). The true cause of otosclerosis is yet to be determined. The author is of the opinion that it is attributable to circumstances which affect the general nervous system or to alterations of the normal condition of the blood and circulatory mechanism. Its onset is often referred to shock, fright, sudden grief, prolonged mental anxiety, affecting the general nervous system; or it may be associated with chlorosis, anemia, severe hemorrhage and parturition. General febrile conditions, especially influenza, may also be associated with the onset.

Bryant in 1910 (1) stated that the general etiological factor in otosclerosis may be toxemia of any kind; autointoxication, rheumatic, gouty, or syphilitic conditions, intoxication by infectious diseases, puerperal and menstrual disturbances. Unbalanced internal secretions of the thyroid and pituitary should also be considered.

In an article in 1911, Mayer developed his theory that the focal disease in the petrous bone characteristic of otosclerosis is produced by local circulatory disturbances of the arteries of the bone. He notes also that this also indicates a further resemblance between otosclerosis and osteitis fibrosa, as Recklinghausen ascribed the latter to circulatory disturbances resulting

from an irritation of the vasomotor nerves and leading to repeated congestion of the bone marrow.

Aside from these functional disturbances of the vasomotor apparatus, organic changes in the blood vessels may also be the cause of the circulatory disturbances that are the basis of the otosclerotic changes. The part played by arteriosclerosis as the cause of the vascular constriction in otosclerosis is suggested by anatomical findings. Furthermore, the same general diseases that are considered to be etiological factors in arteriosclerosis are also regarded as the cause of otosclerosis. Special mention is made in this connection of the acute infectious diseases, more particularly scarlet fever and typhoid fever, diphtheria and influenza (1).

The question has recently been raised, if otosclerosis can be produced or aggravated by a traumatism, and in view of the known origin of atherosclerosis through traumatism, the author (1) regards traumatism as entirely possible as an indirect cause of otosclerosis. Vasomotor neuroses may also follow upon traumatism. Syphilis may enter into consideration as an etiological factor, through the causation of vascular changes, but it is evidently not a frequent cause of otosclerosis.

Denker (1), at the International Otological Congress of 1912, gave his opinion that in the majority of cases

of otosclerosis there is a hereditary disposition to the disease. This predisposition is the foundation upon which the disease arises under the influence of certain irritants. Among these irritants are: increased bone formation during puberty; bony changes during pregnancy and the puerperium probably dependent on the hyperplasia of the hypophysis during pregnancy; and circulatory disturbances such as are present in arteriosclerosis, vasomotor neuritis and syphilis. The author emphasizes the importance of the hypophyseal changes in pregnancy in the etiology of otosclerosis, as shown by the frequent onset or exacerbation of symptoms during pregnancy.

It was discovered by Frey and Orzechowski (1), in 1917, that in latent tetany there was frequently an associated deafness. The authors note that the following characteristics of otosclerosis indicate that it is not merely a local process, but dependent upon pathological conditions in the general organism: (1) Family heredity, which undoubtedly plays an important part. (2) Almost exclusively bilateral occurrence. (3) Frequent beginning of the process soon after puberty or at least between the second and third decade. (4) Frequent onset of the process in women during pregnancy or immediately after delivery; the striking aggravation of otosclerosis by pregnancy. (5) Frequent presence of various vasomotor disturbances. (6)

Occurrence of aggravation after grave psychic trauma. (7) The fact that practically all otosclerotic patients have a certain peculiar body type, which although it has not yet been analyzed in detail, is so distinctly present in the total impression conveyed by the individual.

Rock (1920)(1), working in Siebenmann's Clinic in Basel, studied many unselected cases of otosclerosis for symptoms of latent tetany. Careful otological examination confirmed the diagnosis of otosclerosis in each case, but neurological examination showed no evidence of latent tetany in any case. Rock, therefore, is unable to accept the conclusions of Frey and Orzechowski in regard to the latent tetany and parathyroid insufficiency in otosclerosis.

In regard to Rock's criticism of his work, Frey (1) definitely finds in otosclerotic patients definite evidence of parathyroid deficiency. A point in favor of the endocrine gland influence on otosclerosis is that it occurs most frequently in the female sex in whom the normal processes of sexual life put an especially heavy strain on the endocrine gland system and especially on the thyroid.

Several cases were reported by Fraser (1), in 1918, two from the same family, in which otosclerosis was associated with fragilitas ossium and blue sclerotics. He

these glands is being considered as an etiological factor in otosclerosis. He is of the opinion that the predisposing factor in otosclerosis in congenital bone foci in the labyrinthine capsule, but these foci begin to proliferate only under the influence of certain determining causes, which include a variety of conditions, among which the author mentions puberty, pregnancy, puerperium, catamenia, senility, physical or psychic trauma, as was shown during the war; furthermore, all infectious diseases, acute and chronic otitis, rhinitis, intoxications and the so-called dyscrasias, to which can probably be added also all blood diseases, such as anemia, chlorosis, and leucemia.

From his clinical study of cases of otosclerosis, Pollock (1918)(1) is convinced that altered ductless-gland secretion is an important etiological factor; several authors agree that focal infection plays an important part in the etiology of otosclerosis. Pollock suggests that focal infection acts through the ductless glands.

The undeniable pathological resemblance between otosclerosis and osteomalacia and rickets was noted by Muller in 1920 (1). The author agrees with Bryant and Ferreri on this point. In both of these diseases, the influence of the glands of internal secretion may be assumed as an etiological factor.

A case of a boy who had had seven bone fractures

since three years of age and which was due to trauma was reported by Nager in 1921 (1). For the next few years, there had been progressive deafness. The sclerae in this case were blue. Functional tests showed the deafness to be of the otosclerotic type. This symptom complex of fragility of the bones, blue sclerae and otosclerosis has been noted in a few other cases reported in recent literature.

Kauffman (1932)(1) points out that various investigators have shown that the changes in the temporal bone in rickets are not dissimilar in their processes to those in otosclerosis, although the end-results are not entirely identical. It is known that rickets is essentially a deficiency disease due primarily to a deficiency in fat-soluble vitamin "A". It seems a reasonal assumption that a similar deficiency acting throughout a different period of life may produce not infantile rickets, but bony changes elsewhere, as in otosclerosis.

On the basis of this hypothesis, Kauffman (1) and his associates, made experiments on young rats fed upon two types of deficiency diets, one deficient in fat-soluble vitamin only and one deficient in both fat-soluble vitamin and calcium, in comparison with normal controls on a balanced diet. The rats were killed at the end of a three months' experimental period and a special study

made of the changes in the bony labyrinthine capsule. Their findings indicate that ototsclerosis may be a result of rickets or of a dietary deficiency similar to that which causes rickets still existant during adult life.

The determination of the calcium content of the blood serum in cases of otosclerosis was reported by Leicher in 1922 (1). In seventy five per cent the blood calcium was found to be diminished below the level of the normal range of variation. For an etiological explanation of the diminished serum calcium in otosclerosis, the author naturally considers the influence of the endocrine glands, in view of the frequent occurrence of otosclerosis during puberty, and its frequent origin and aggravation during pregnancy.

From his study of otosclerosis, Delie (1923)(1) concludes that otosclerosis, like sclerosis elsewhere in the body, is due to disturbances of the circulation. The circulation is controlled largely by the sympathetic nervous system, and this in turn is controlled by the ductless glands, and especially the thyroid. A deficiency in the thyroid secretion causes an overstimulation of the sympathetic a sympathicotonia.

In a study of the blood cholesterin in various conditions, Berberick (1924)(1) determined the blood choles-

terin in many cases of otosclerosis and found it to be reduced to one-half to one-tenth the normal.

According to Manasse, two kinds of foreign deposits are occasionally seen within the bone in otherwise entirely normal petrous bones, at the anterior margin of the oval window, the site of predilection of the otosclerotic affection: (1) cartilage; (2) fatty marrow. Manasse himself surmises that these deposits are connected with the otosclerosis. As cartilage and fatty marrow very easily store cholesterins, the possibility of a cholesterin deposit in this tissue in otosclerosis cannot be denied, and this cholesterin may prove of importance for the further development of these foci, in a similar way as cholesterin deposits in other parts of the body (1).

Kopetzky and Almour (1925)(1) made a study of the calcium content of the blood in cases of deafness and found that the greatest number of cases in which the calcium content of the blood was decreased corresponded with those that were diagnosed clinically as otosclerosis. These findings support the theory that calcium deficiency is a factor in the production of otosclerosis.

Thirty-two cases of otosclerosis were reported by Stein (1) in 1925 in which he had made a special study of the effect of pregnancy on the symptoms. The author concludes that pregnancy is undoubtedly capable of eli-

citing the otosclerotic symptoms and of causing the advance of the disease when present. As to the premature interruption of the pregnancy, Stein thinks that it is capable of arresting the otosclerotic process. If the pregnancy has been terminated in the first weeks, an improvement of the hearing capacity may even be expected. In all the cases studied by the author, the subjective symptoms showed a considerable modification after the termination of the pregnancy and not uncommonly disappeared entirely; the hearing capacity was preserved in some cases for a number of years.

In 1926, Brunner (1) expressed the opinion that the ultimate cause of otosclerosis must be sought in functional changes of the endocrine glands. Besides this inherited inferiority of the organism, the occurrence of otosclerosis requires another pathological factor, in the form of metabolic disturbances that are still obscure.

Drury (1) summarizes his observations thus: "Many and widely divergent factors can excite the appearance of otosclerosis in predisposed persons. The essential factor underlying the morbid change is possibly a chemical one affecting the nutritive stability of developing and fully developed bone and cartilage. In a dominant percentage of cases the several endocrine glands are di-

rect etiological factors through their influence on metabolism. The constitutional tendency or hereditary influence would seem to be a dominant factor in determining the condition of otosclerosis where an endocrine or a non-endocrine pathology produces disturbances of metabolism. The work so far done is to be regarded as suggestive rather than definitive of a possible ultimate solution of the highly complex problem of the etiology of otosclerosis."

A review of the theories of the etiology of otosclerosis was presented by Simeoni (1) in 1927; in common with many others, especially recent investigators, he is of the opinion that the development of the pathological lesions in otosclerosis depends upon an impairment of the calcium metabolism.

In 1928, Lindeman (1) reported the determination of the blood calcium in twenty-five cases of otosclerosis. He found the value within the accepted limits of normal, except in two cases. The author notes that his findings are not in accord with those of other recent investigators.

Malherbe (1) (1928) is of the opinion that the peculiarities of ossification of the labyrinthine capsule and site of the points of ossification determine the localization of the foci in otosclerosis, but that the

cause of the development of these foci is a latent tuberculous infection on the basis of a familial tuberculous diathesis. The tuberculous infection in these cases, the author believes, acts upon the bone through the medium of the endocrine glands that control osteogenesis.

In his 1928 article on otitis insidiosa in which he includes all forms of non-specific progressive deafness including otosclerosis, Bryant (1) states that the etiological factors are focal infection, endocrine dysfunction, and hereditary tendency.

The data that Davenport has reviewed indicate some of the influences of external conditions. Foremost is, in the female, pregnancy. This tends frequently to exaggerate the symptoms, sometimes permanently, sometimes temporarily, with even an improvement in hearing between pregnancies. In some cases, however, it is stated that pregnancy did not affect the symptoms.

The next most common associated condition is nasal "catarrh." Indeed otosclerosis formerly, in many places, bore the name "dry catarrh." While it is easily understandable that infection of the nasal passages, including the eustachian tube, may lead to otitis media, it is not so easy to see why it so often accompanies otosclerosis. Davenport states that it possibly is the tendency toward

imperfect bone formation of the otic capsule to extend also to the nasal conchae and ethmoid, causing partial obstruction of the passage and favoring infection. (2)

Other external conditions that are believed to have "brought on" otosclerosis or to exaggerate its symptoms are: colds, scarlet fever, influenza, a high dry location and the use of quinine. These can hardly be regarded as sufficient causes for otosclerosis, but merely as external conditions modifying its progress.

In a review of literature by Dickie (3), he states that Gottlieb has made interesting studies on pancreatic function in cases of otosclerosis and Gottlieb suggests the possibility that a defect in pancreatic digestion may stand in casual relation to the deterioration in hearing. He also stated that deafness is the rule in diabetes.

In an original and stimulating paper on otosclerosis, Louis Mirvish (1930) (8) supported the view that this disease is a metabolic disorder. He reviewed the present state of knowledge, pointing out the frequency of gonadal deficiency, low calcium content and cholesterol metabolism, etc. Previous work by Mirvish and Bosman had established the fact that extract of ovary injected into animals produces a fall in blood calcium. They found a substance which is present in extracts of ovary, suprarenal cortex and probably of testis and which reduces the blood

calcium both in rabbits and man. More recently, Mirvish had found such a substance present in cereals, especially oatmeal. This substance has the effect of neutralizing vitamin D.

Mirvish considers that there is a close analogy between rickets, osteomalacia, and otosclerosis, and that similar treatment should be used for all three.

Fowler (3) (4) reported fifty-eight cases of otosclerosis that he had had under observation in the preceding two years. In every case estimations of the blood calcium, phosphorus and cholesterol were made. His results differed from those of many other observers in that the calcium content of the blood was practically identical with that in forty-four normal controls. He stated that it appears certain that in established cases of otosclerosis no changes of consequence can be detected in the calcium-phosphorus variations of the blood.(5)

Breitman (1933) (3) (4) in one of his papers discusses the question of an endocrine disturbances as the basis for otosclerosis. When there are endocrine disturbances associated with otosclerosis, the disturbances probably have the same origin as the otosclerosis, namely, a degenerative state. They are not necessarily the cause of the otosclerosis, but are merely another result of the same underlying condition. Breitman found in a

large series of experiments that the blood calcium is either normal or increased. He has been unable to find any sign of parathyroid insufficiency. He obtained normal or increased cholesterol figures in the serum. According to Breitman, the idea of an endocrine disturbance as the cause of otosclerosis rests on a very superficial diagnosis in most cases.

The literature for 1936,(as reviewed by Shambaugh) (10), contains the usual number of reports of attempts to connect otosclerosis with metabolic, endocrine or vitamin disturbances.

From France come two reports (10) purporting to show the connection of otosclerosis with the parathyroid glands. Because alterations in calcium metabolism in otosclerosis have been reported in the literature and because the parathyroid glands regulate the blood calcium level, J. M. Alonso and A. Chiarino removed one parathyroid gland or tied the terminal branches of the inferior thyroid artery on one side in seven patients with otosclerosis and obtained a slight improvement in hearing in six of the seven. Having found a relation between otosclerosis and tuberculosis, the same authors then used an antituberculosis vaccine in some cases of otosclerosis and obtained improvement in hearing. Finally, they tried calcium and irradiated ergosterol in treating otosclerosis, and again im-

provement in hearing resulted.

A. Malherbe (10), assuming that otosclerosis is due to a lack of parathyroid secretion, obtained a striking improvement in hearing after the administration of parathyroid extract to patients with otosclerosis. This author, therefore, neatly contradicts Alonso and Chiarino, who improved the hearing by removing one parathyroid gland!

Equally unconvincing is a paper by E. Charschak (10), who improved the hearing in several cases of otosclerosis, with disappearance of tinnitus, by the oral administration of irradiated brewers' yeast, thus combining vitamin B with vitamin D.

From the Leningrad Institute for the Throat, Nose and Ear, S. M. Scheschko (10) reports a noticeable diminution of the blood chlorides in all of seventy-eight cases of otosclerosis studied. The author sees in this lowered chloride content an indication of chemical indolence of the cells, pointing to a diminished immunobiologic state of the organism which may serve as an etiologic basis for the development of otosclerosis. Other Russians have studied the potassium and calcium content of the blood in otosclerosis, also the total nitrogen content of the blood serum and interpret their findings as evidence of a generalized metabolic disturbance. These reports from the Russian

literature are similar in that the authors obtained positive results in finding an abnormal blood chemistry in otosclerosis, whereas similar studies previously carried out elsewhere have generally given entirely negative results. Did these authors have a more accurate method of measuring the blood chlorides, calcium, potassium and nitrogen than previous workers, or did their desire to obtain positive findings outbalance their desire to determine the actual facts?

Another metabolic study of otosclerosis is reported by G. Orso (10) from Hungary, who made nasal metabolic tests in otosclerotic patients. Most of the cases showed an elevation of from 15.3 per cent to 57.6 per cent, although only two of these cases had other symptoms of exophthalmic goiter. The author believes that the elevated metabolism is primary in otosclerosis and that by the early use of iodine the condition can be arrested or improved. This surprising report is as hard to believe as the reports from Russia.

Gray (6) states that several investigators have put forward the view that otosclerosis arises from some defect in one or more of the internal secretions of the body. It is very difficult either to prove or disprove such theories, but one point which would appear to throw great doubt upon their value is the fact that many patients de-

velop otosclerosis when they are in the best of health. Still this argument against these theories must not be allowed to carry too much weight. A very minor deficiency or excess of one of the hormones might conceivably be sufficient to affect the organ of hearing without other wise perceptibly affecting the general health.

One by one, the incriminated glands, after the most careful laboratory research as well as clinical observation, now apparently stand acquitted of primary responsibility; although it is entirely plausible that certain internal secretions may be altered and invested with pathogenic properties through an original metabolic disturbance.

SUMMARY

Up to the time of Toynbee in 1851 the history of otosclerosis is a collection of fragmentary bits of anatomy and physiology, some correct and some incorrect, but all leading to a basic knowledge essential to later studies. From the time of his first theory of "rheumatoid arthritis" as being the cause of stapes ankylosis, many theories have been evolved.

At the present time there are probably seven main theories as to the etiology of otosclerosis:

1. Hereditary, which seems to be regarded as the one constant factor in its etiology.

2. Infectious theory, more in the disregard, though some otologists advise removal of all foci of infection.

3. Toxic theory, intestinal autointoxication, gouty diathesis and a uric acid diathesis.

4. Deficiency theory, a question of vitamins, brings out analogies to rickets, osteomalacia, arthritis deformans and similar conditions.

5. Endocrine theory, more recent, received its impetus from the observing evidence of deafness and latent tetany.

6. The circulatory stagnation theory, states that a

failure of local blood supply results in the absorption of normal bone and cartilage, and results in spongy bone and later a deposition of lime salts.

7. The neoplastic theory, states that because of a faulty anlage with or without an exciting cause, lesions which are essentially new growths develop in a highly complex embryological portion of the labyrinthine capsule.

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