The inheritance of otosclerosis

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The hereditary nature of this common disease has been recognized for about a century (Toynbee, 1861; Magnus, 1876), yet the simple mode of inheritance has almost escaped recognition amid the bewildering variety of postulated theories, all striving to adhere to strict Mendelian ratios.

A major confusion has arisen from the assumption that otosclerosis is twice as common in females as in males. This led Bauer and Stein (1925) to suspect a double recessive inheritance; Davenport *et al.* (1933) to claim a double dominant inheritance, one factor being sex-linked; and Hernandez-Orozco and Courtney (1964) to invoke two interacting genes, one dominant and sex-linked, the other autosomal and recessive. Larsson (1960) and Morrison (1967) have shown that otosclerosis is equally common in the two sexes and that, in the majority of families, the disease has a simple autosomal dominant inheritance with incomplete manifestation. This incomplete manifestation or penetrance, causing difficulty in identifying the genotype, has been the other major problem.

In 1944 Guild published his microscopic findings from over a thousand autopsy temporal bones, and this work has befogged the genetic picture and discouraged simple clinical research for the past twenty years. Guild admitted that his results made it difficult or impossible to determine the type of inheritance. The implications of his work will be discussed below.

A further complicating factor has been the argument that otosclerosis is a local manifestation of osteogenesis imperfecta, and that both conditions are based on a common genetic abnormality (Wullstein *et al.*, 1960: and Ogilvie and Hall, 1962).

In an attempt to unravel some of these problems a genetic and clinical survey was conducted in East London between 1961 and 1964. This brief review summarizes the main findings and conclusions, and offers a new theory to correlate the frequencies of clinical and histological otosclerosis. It also examines sporadic cases in more detail.

A consecutive group of 150 otosclerotic patients was investigated, detailed family histories were taken and the examination of deaf relatives arranged, the maximum diagnostic effort being directed towards siblings and parents. There had to be no doubt about the diagnosis and all suspect cases were excluded, both during selection of propositi and later when examining other family members. Phenocopies encountered included Paget's disease of bone, congenital stapedial abnormalities, traumatic

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ossicular lesions, rheumatoid arthritis, chronic adhesive otitis, ossicular discontinuity or fixation and sub-total deafness.

The 150 propositi came from 146 sibships of which two were found twice and one ascertained three times. Excluding propositi, there were 308 ascertained secondary cases of otosclerosis among these families (Table I).

TABLE I.

OTOSCLEROTIC FAMILY MEMBERS.

	Propositi	Parents (64) Children (7)	Grand-parents	Aunts, uncles nephews and nieces (100) Cousins (18)	Siblings	Totals
Diagnosis confirmed ..	150	34	3	44	53	284
Dead	—	32	40	31	8	111
Not examined ..	—	5	1	43	14	63
Totals	150	71	44	118	75	458

Mode of inheritance

In the majority of families the evidence in favour of an autosomal dominant inheritance is conclusive. Of the 146 sibships under study, 43 contained isolated cases, in a further 4 otosclerosis was confined to the sibship, while in 99 (68 per cent) there were secondary cases outside the sibship. In 54 of these the propositi had received the gene from one parent, in 5 both parents had otosclerosis, and in 40 families (though the parents were normal) other relatives such as grandparents, uncles, aunts, nephews, nieces or first cousins were affected on one side of the family only. There were no cousin marriages among the parents of propositi.

In two families the disease was traced through four generations, in 42 families through three generations, and in 55 families through two generations. In the 5 sibships where both parents were affected, there was no difference between the homozygous and heterozygous otosclerotic subjects which could be demonstrated clinically, operatively or histologically. This is a classical characteristic of dominant inheritance.

The scatter of secondary cases throughout these pedigrees also points to a simple dominant inheritance. If the abnormal gene were always manifest, half the siblings, parents and children would be affected; a quarter of the grandparents, grandchildren, and other second degree relatives would have otosclerosis; and an eighth of first cousins would be involved. In fact the observed ratios were 1/4·5, 1/9·5 and 1/20·7. These ratios are almost in the same proportion as 1/2: 1/4: 1/8, and confirm the mode of inheritance.

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It is obvious that the genotype (those carrying the abnormal gene) does not always represent the phenotype (those with clinical otosclerosis), but the distribution of secondary cases indicates the degree of manifestation in otosclerosis to be almost a half. In fact 43 per cent of those carrying the abnormal allele develop the clinical entity (Table II). The other 57 per cent are likely to have histological otosclerosic foci without stapedial ankylosis and deafness, though they can also transmit the disease.

TABLE II.
MANIFESTATIONS IN OTOSCLEROSIS.

Relationship to propositi	Number affected	Number normal	Total	Expected ratio	Expected affected	Degree of manifestation (per cent)
Parents	64	228	292	$\frac{1}{2}$	146	43·8
Grandparents ..	44	361	405	$\frac{1}{4}$	101·25	43·4
Aunts, uncles, nephews, nieces ..	100	864	964	$\frac{1}{4}$	241	41·5
Children	7	19	26	$\frac{1}{2}$	13	53·8
Siblings excluding propositi and sporadic families ..	75	250	325	$\frac{1}{2}$	162·5	46·1
Cousins	18	355	373	$\frac{1}{8}$	46·6	38·6
Totals	308				710·35	43·3

Variable expressivity

Clinical severity must not be confused with manifestation which follows the all or none law. Once the gene for otosclerosis is manifest any degree of clinical severity may be encountered. As would be expected with an hereditary disease, the variable expressivity was mainly between and not within families. There was a striking similarity in the age of onset of deafness and rapidity of its progress in any given family. This was especially noted within sibships but was less obvious from one generation to the next. The concordance in monozygotic twins has been noted (Larsson, 1960), and familial ipsilateral otosclerosis and familial asymmetry of deafness are other examples of this expressivity (Morrison, 1967).

In terms of simple genetic counselling it can therefore be said that, if two otosclerotic parents have issue about half of their children will develop the disease; and if an otosclerotic marries a non-otosclerotic about a quarter of their offspring will have clinical otosclerosis. Furthermore, in both mating types, the severity of the disease is likely to be the same as in other family members.

Partial sex limitation

It is common clinical knowledge to otologists that otosclerosis is encountered more frequently in females than in males and a sex ratio

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of about two to one has been noted by most authorities. These observations, however, relate to out-patient or surgical experience and do not reflect the true sex ratio of the disease. There are several reasons for this apparent contradiction.

Reference to Table III demonstrates that, in the 146 sibships studied, 40·5 per cent of the females (137 out of 338) were affected and 32·0 per cent of the males (88 out of 275). This approximates to the 1/1 sex ratio that would be expected with an autosomal dominant inheritance. In fact, otosclerosis is not twice as frequent in females, though this impression is partly given by the increasing proportion of females in any population of advancing years coupled with the increasing disability of otosclerotic deafness with the passage of time.

TABLE III.

SEX RATIO IN OTOSCLEROSIS.

	Otosclerotic siblings	Normal siblings	Totals
Females	137 (Expected 124·1)	201 (Expected 213·9)	338
Males	88 (Expected 100·9)	187 (Expected 174·1)	275
Totals	225	388	613

Σchi ^{2} (corrected) = 4·36
D.F. = 1
P = 0·05

Some partial sex limitation to the female is apparent in these figures and the sex ratio difference is just significant at the 5 per cent level.

These sibship data can be examined in another way. If otosclerosis were twice as frequent in females, then a 2/1 ratio would be expected among secondary cases. But when propositi are excluded the sex ratio becomes exactly equal. These sibships were ascertained, after all, from out-patient experience and there were almost twice as many female propositi to produce this bias.

Females with otosclerosis are more likely to seek medical advice than their male counterparts because, firstly the disease advances more rapidly in females during the first twenty years of deafness (this is, in measure, due to the hormonal effects of pregnancy); secondly unilateral otosclerosis or definite asymmetry of deafness is much commoner in males (20 per cent of male cases) than in females (9 per cent of female cases); and thirdly the male, working and living in a noisier environment, is less likely to be aware of his disability.

Sporadic otosclerosis

Only after detailed inquiry can otosclerosis be classified as isolated or sporadic. Not infrequently the existence of other deaf relatives is

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denied at the first interview but is subsequently forthcoming. There are four possible explanations for the occurrence of isolated cases, which represent about 30 per cent of patients with this deafness.

(a) They may be phenocopies of the disease. These deafnesses simulating otosclerosis can be readily excluded by adequate investigation and tympanotomy but, without surgical exploration, the relatively common acquired or the rarer congenital ossicular fixations or defects cannot be diagnosed with certainty.

(b) They may represent new mutations. Morrison (1967) has shown that 1·4 per cent of the alleles for otosclerosis are dropped per generation and that, assuming genetic equilibrium, 2 out of every 150 will be due to this cause. New mutations, calculated at a frequency of less than 50×10^{-6}, can account for only a small fraction of these isolated cases.

(c) It would seem reasonable to suppose that, since only 43 per cent of individuals carrying the abnormal dominant gene develop clinical deafness, these sporadic cases are due to failure of manifestation in other family members (though they might be expected to have histological foci). This, at first inspection, seems the simplest way of explaining the majority of these patients, but it fails to concur with Guild's (1944) evidence of the frequence of histological otosclerosis.

(d) The fourth hypothesis, which will now be pursued in more detail, envisages these isolated cases as arising from a different mode of inheritance.

This phenomenon of similar phenotypes produced by different genetic mechanisms occurs with other hereditary diseases in man, perhaps the best example being the varying types of perceptive 'deaf-mutism', some dominant, some recessive and others sex-linked (Fraser, 1964). It is also encountered in a variety of other conditions such as the hereditary ataxias and muscular dystrophies, Hurler's syndrome, diabetes insipidus, retinitis pigmentosa, ichthyosis and cleft-palate deformities. The evidence from other genetic abnormalities makes this theory quite tenable, and the most likely alternative would be two autosomal recessive alleles in homozygous state producing clinical otosclerosis. The heterozygous 'carrier state' might result in areas of histological otosclerosis without stapedial ankylosis.

Before proceeding with the argument and discussing its statistical aspects in detail, it is necessary to re-examine the work of Guild published in 1944, for since then there has been no similar study of such size. Table IV summarizes the number of temporal bones sectioned and examined by Guild and indicates the distribution of all histological otosclerotic foci which he described. Among male and female Caucasians the overall incidence was 7·52 per cent (44 foci out of 585) and over the age of twenty years it was 8·33 per cent (38 foci out of 456). Eighty per cent of these foci were in relation to the fissula ante fenestram.

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TABLE IV.

INCIDENCE OF 'HISTOLOGICAL OTOSCLEROSIS' FROM S.R. GUILD NUMBERS WITH OTOSCLEROTIC FOCI SHOWN IN PARENTHESIS.

Age	Totals	White male	White female	Negro male	Negro female
<5	161 (1)	37 (1)	30 (0)	48 (0)	46 (0)
5–9	26 (1)	8 (0)	9 (1)	5 (0)	4 (0)
10–14	33 (2)	13 (0)	6 (2)	5 (0)	9 (0)
15–19	55 (2)	14 (0)	12 (2)	16 (0)	13 (0)
20–29	151 (3)	35 (2)	22 (0)	55 (1)	39 (0)
30–39	176 (10)	48 (4)	40 (5)	62 (1)	26 (0)
40–49	210 (17)	77 (8)	25 (7)	86 (1)	22 (1)
50–59	175 (5)	67 (3)	21 (1)	76 (1)	11 (0)
60–69	121 (6)	61 (4)	21 (2)	29 (0)	10 (0)
70+	53 (2)	32 (2)	7 (0)	13 (0)	1 (0)
Totals	1,161 (49)	392 (24)	193 (20)	395 (4)	181 (1)

There can be no doubt that histological otosclerosis (the genotype) occurs in the absence of clinical otosclerosis (the phenotype). The difficulty is to correlate the frequency of the one to the other. Some of the 'foci' scored by Guild may have been areas of normal osteoblastic activity in relation to the several fibro-cartilaginous rests which occur even in the adult temporal bone, but having made some allowance for this possible error there is still a large discrepancy between the Caucasian incidence of clinical otosclerosis—3 per 1,000—and of histological otosclerosis—say 70 per 1,000 (7 per cent).

If Guild's results are accepted, this relationship can be explained on two assumptions, namely that sporadic cases are due to a recessive inheritance and that the heterozygous state results in an area of histological otosclerosis whether this 'carrier state' pertains to either a recessive, or a non-manifest dominant gene. There is, after all, little difference between the two as the effect must be suppressed by other modifying genes.

The great majority of patients with otosclerosis are not handicapped by deafness until well into adult life, and it seems likely that random mating is taking place and that there is neither selection for nor against the gene for otosclerosis. In this event the two contrasting alleles in the population, p and q, should remain constant and their sum must be unity. The square of their sum, $(p + q)^2$ or $p^2 + 2pq + q^2$ will also total one, and p^2 and q^2 will represent the two homozygous frequencies in the population while 2pq will represent the heterozygous.

From the clinical data of this recent survey, and on the assumption that isolated cases follow a recessive inheritance, the theoretical incidence of histological otosclerosis can now be calculated.

$$\text{The Incidence of Clinical Otosclerosis} = \frac{3}{1{,}000}$$

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The Proportion of Isolated Cases $= \frac{3}{10}$

$\therefore$ The Incidence of Isolated Otosclerosis $(q^2) = \frac{9}{10{,}000}$ (a)

Therefore $q = \frac{3}{100}$ and since $p + q = 1$

Then $p = 1 - \frac{3}{100} = \frac{97}{100}$

The frequence of the heterozygous state

$$= 2pq = 2 \times \frac{97}{100} \times \frac{3}{100} = \frac{582}{10{,}000} \quad \text{(b)}$$

The Incidence of Clinical Otosclerosis $= \frac{3}{1{,}000}$

The Proportion with a Dominant Inheritance $= \frac{7}{10}$

$\therefore$ The Incidence of 'Dominant' Otosclerosis $= \frac{21}{10{,}000}$

Because the Dominant Gene is Manifest in 43%

The Incidence of the Dominant Genotype

$$= \frac{21}{10{,}000} + \frac{29}{10{,}000} = \frac{50}{10{,}000} \quad \text{(c)}$$

The effect of new mutations upon the incidence of histological otosclerosis will be minute, but for the sake of completeness is included. For the Recessive group the Mutation Rate $(M) = f\,(1 - F)$, where f is the frequency of the disease and F the relative fitness.

$$M = \frac{9}{10{,}000} \quad (1 - 0{\cdot}986)$$

$$= \frac{0{\cdot}126}{10{,}000} \text{ or } 12{\cdot}6 \times 10^{-6} \quad \text{(d)}$$

For the Dominant State $M = \frac{1}{2} f\,(1 - F)$

$$= \frac{1}{2} \times \frac{50}{10{,}000} \times (1 - 0{\cdot}986)$$

$$= \frac{0{\cdot}350}{10{,}000} \text{ or } 35 \times 10^{-6} \quad \text{(e)}$$

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The frequency of histological otosclerosis will represent the sum of a, b, c, d and e. This is 641·476 per 10,000 or 6·415 per cent, a figure which does not differ significantly from the frequency recorded by Guild.

It should be emphasized that this is a theoretical consideration, and that arguments against autosomal recessive inheritance can be made. In this survey there were 43 isolated cases and a further 4 with otosclerosis confined to the sibship. A larger number of affected siblings, approaching the 1 to 4 ratio, might be expected. Their absence can only be explained by some form of multifactorial inheritance in this group of patients.

The absence of cousin marriages among the parents of sporadic cases is not very significant when such a common disorder is under consideration. The frequency of the heterozygous or carrier state of otosclerosis in the population would be approximately 1 in 17. With recessive inheritance the chances of an affected offspring from a first cousin marriage are 1 in 8, and therefore first cousin marriages would only double the natural risks of producing affected individuals.

Severity of sporadic otosclerosis

Penrose (1936), discussing dominant conditions which are not fully penetrant, shows that sporadic cases due to new mutations are more severe than the obvious hereditary cases and suggests that there may be non-allelic modifying genes, uneven segregation of which cause this severity. There is no evidence of this in sporadic otosclerosis. The severity of otosclerosis in 123 sporadic cases was compared with that of obvious dominant cases and no difference was found. Two graphs were made charting the mean bilateral hearing loss against the duration of deafness and there was conformity between sporadic and familial cases for both males and females.

Parental age and birth order in isolated cases

The mean maternal age in 64 isolated cases, born 1920 and later, is compared with the expected maternal age figures given by the Registrar General for the years 1921, 1931, 1938 and 1948. The results are shown in Table V. There is no significant deviation from expected. The overall mean maternal age is 30·6 years which is the same as expected.

Paternal age in the population is not given for the years concerned, but there are yearly tables available in which husband's age is given against wife's age, at time of marriage. The differences thus obtained, between husbands' and wives' ages, agree very well with the differences between mothers' and fathers' ages, which are given from 1962 onwards, apart from the wifely age group of 40, and over, where the age of husbands is higher than the age of fathers (see Bundey and Evans, 1969 for fuller explanation). The results, on 64 cases, are compared in Table VI, with

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TABLE V.

MEAN AGE OF MOTHER SPORADIC OTOSCLEROSIS.

Years	Mean maternal age (Registrar General)	Mean maternal age (otosclerosis)		Years
1921	30·6	31·3	(28)*	1920–28
1931	31·7	29·9	(22)	1929–35
1938	29·1	30·7	(12)	1936–45
1948	28·8	31·0	(2)	1946–50
Overall	30·6	30·6	(S.D 5·6)	Overall

*Number in brackets refers to number of cases in each age group.

the husbands' age expected, over the period 1920–1948. There is no significant deviation from expected, and overall, the mean paternal age of our cases is 32·4 years (S.E. 0·838), compared to an expected mean paternal age, standardized from mother's age, of 32·7 years.

TABLE VI.

MEAN AGE OF HUSBAND SPORADIC OTOSCLEROSIS.

Age of wife	1920	1928	1938	1948	Mean 1920–48	S.D.	Otosclerosis cases 1920–50
<20	23·12	23·06	23·63	23·59	23·35	3·59	21·0 (1)†
20–24	25·31	25·18	25·84	25·50	25·46	3·99	25·7 (8)
25–29	28·95	28·29	28·90	29·51	28·91	5·00	28·2 (17)
30–34	33·56	32·48	33·49	34·59	33·53	6·75	34·8 (23)
35–39	39·26	37·09	39·46	39·29	38·77	8·16	37·7 (11)
40–50	47·12	43·93	48·29	47·36	46·67*	9·26	39·7 (4)

*This figure is too high. The corresponding age for fathers in the years 1962–66 is 43·8 years.
†The number in brackets gives the number of cases in each age group.

Birth order figures are not available prior to 1938, so a direct population comparison with the cases of otosclerosis has not been possible. Therefore, on 123 isolated cases, a within family analysis of birth rank, as developed by Greenwood and Yule (1914), and Penrose (1934), has been performed. In this method the expected distribution of birth rank of isolated cases, is obtaining by scoring number in family whose otosclerotic state is known for each birth rank in turn. In this way it is possible to obtain an expected distribution of number of cases in each birth rank, which can then be compared to the observed distribution. Table VII shows this comparison. There is a consistent tendency for later birth ranks to be associated with more cases of otosclerosis. This is significant at the 5 per cent level ($X^2 = 10 \cdot 92$ on 5 d.f. in the one-tailed test distribution).

Since both maternal and paternal ages do not differ from the expected, this tendency for sporadic cases of otosclerosis to arise from later births

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must be due to either parity or environmental factors. The sex ratio in sporadic cases is exactly equal.

TABLE VII.

BIRTH RANK SPORADIC OTOSCLEROSIS.

	1st	2nd	3rd	4th	5th	6th +	Total
Expected number of affected	34·40	30·03	20·22	14·98	10·56	12·81	123
Observed	24	24	24	16	16	19	123

$\chi^2 = 10{\cdot}92$ d.f. $= 5$ $\quad 0{\cdot}05 > P > 0{\cdot}01$ one-tailed distribution.

Other genetic factors

There was no evidence of either association or genetic linkage between otosclerosis and the ABO, MN and Rhesus blood groups, the secretor status or the haptoglobin genotypes in these otosclerotic families. There was, however, a statistically significant association with the ability to taste phenylthiocarbamide though, at present, this cannot be explained in biochemical language. No association was found between hair or iris colour and otosclerosis.

Chromosome studies in otosclerosis and in osteogenesis imperfecta demonstrated normal karyotypes.

Osteogenesis imperfecta and otosclerosis

In order to understand the proper relationship between these two hereditary disorders of collagen and to introduce perspective into the discussion, the problem must be examined on the basis of each to the other.

Just as there are many grades of severity of osteogenesis ranging from foetal death, to a number of fractures induced by trivial trauma in childhood, likewise there are varying degrees of severity of otosclerosis in different families, the more marked having an adolescent onset and rapid progress. If the two conditions were due to the same abnormal allele, modified by other genes, as favoured by Stoller (1962), then intermediate families would be expected to present with some fractures, blue sclerae and the early onset of deafness.

Yet from 240 otosclerotic families investigated there was no evidence of such intermediate cases and only one family was encountered with blue sclerae affecting some of its members, and incidence of less than half per cent. Furthermore osteogenesis often manifests itself as a widespread collagen disease involving bone, joints, sclerae, teeth, blood vessels and possibly skin. There was no evidence of skeletal abnormalities, of the characteristic hereditary opalescent dentine, nor of any haemorrhagic diathesis in these otosclerotic patients.

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From the point of view of otosclerosis, therefore, there is no evidence to relate the two diseases in the language of clinical genetics. It must be remembered that blue sclerotics, though classically associated with fragilitas ossium, occur as an isolated familial disorder, and also in association with Marfan's Syndrome (McKusick, 1955) as well as with otosclerosis.

The deafness encountered in osteogenesis imperfecta and the temporal bone pathology in that condition have been the principal factors responsible for claims of identity with otosclerosis. Similar reasoning could be presented for osteitis deformans (Paget's Disease of bone), osteitis fibrosa cystica and the fibrous dysplasias of the skull, which occasionally involve the temporal bone. The pathological changes are similar in all and much more widespread than in otosclerosis. Recent studies by Clerc and Chevance (1965), involving several specialized staining techniques, have shown significant differences in the microscopic pathology of the stapes footplate in otosclerosis and in osteogenesis. These workers conclude that the two conditions have a different pathological basis, despite their superficial similarity. Microscopic fractures of the footplate and subsequent healing are considered an important cause of the stapedovestibular ankylosis in osteogenesis imperfecta, Altmann and Kornfeld (1967), from histological and histochemical evidence, also consider them to be different diseases.

About half the children with osteogenesis imperfecta, with or without blue sclerae, who survive into adult life develop deafness which is clinically similar to otosclerosis, though in osteogenesis almost half the deaf subjects have a severe sensori-neural loss of a type which is less frequently encountered in otosclerosis and usually after many decades of progressive hearing loss. From a clinical and genetic point of view the deafness in these subjects with osteogenesis could be a simple phenocopy of otosclerosis; and there is no evidence to invoke any complicated multifactional inheritance or genetic linkage.

From the otological view point the important and informative family members would be those *with deafness*, with or without abnormal sclerae, who had *not* fragilitas ossium. In an extensive investigation, in Sweden, Smårs (1961) found no such members, but his studies were not primarily concerned with deafness.

A search was made among families with osteogenesis in East London and all deaf and living members were examined. Of 21 patients with multiple fractures, 11 had deafness—as already indicated this group could be phenocopies of otosclerosis. There were 5 deaf members who had not suffered from multiple fractures. One child had spastic diplegia and deafness from birth, and two adults had bilateral chronic dry tympanic perforation—none of these three simulated otosclerosis. Two young sisters with blue sclerae however, had deafness suggesting otosclerosis

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though the hearing losses were severe even before puberty—a rare phenomenon even in otosclerotic families with a poor prognosis.

The clinico-genetic proof relating otosclerosis to osteogenesis imperfecta is therefore very scanty. There is no evidence that these conditions are due to the same abnormal allele, but they probably belong to the same family of diseases—the inherited collagen abnormalities. These collagen defects have an autosomal dominant inheritance showing incomplete manifestation and variable expressivity of clinical severity. They may have similar abnormal enzyme systems.

Otosclerosis is a very common disease, osteogenesis imperfecta a relative rarity and, on existing evidence, the deafness in osteogenesis can most correctly be described as a genocopy of otosclerosis.

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