DEPARTMENT OF HEALTH & HUMAN SERVICES

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Centers for Disease Control
Atlanta, Georgia 30333

Refer: FL-119
June 1982

ADULT FLUORIDE THERAPY

Two recent studies have demonstrated some dramatic results from the use of therapeutic levels of fluoride in the treatment of osteoporosis and otospongiosis. Although this research does not have any relationship to community water fluoridation, both studies demonstrate the effectiveness and safety of administering high levels of fluoride to elderly populations over many years of treatment.

Study Highlights ("Effect of Fluoride/Calcium Regimen on Vertebral Fracture Occurrence in Postmenopausal Osteoporosis"--copy enclosed):

- Five-year followup of 165 women, age 50 to 81, ranked various treatment regimens, including calcium, vitamin D, estrogen, and fluoride.

- The addition of fluoride to the conventional treatment regimen reduced the number of fractures by 30 percent.

- Sixty percent of the fluoride-treated patients had increased bone mass and one-seventh the fracture rate of fluoride-deficient regimens.

- Fluoride doses of 50-60 mg/day could not be tolerated by all patients; however, adverse reactions were also observed from therapeutic levels of vitamin D, a treatment which was not efficacious.

Study Highlights ("Enzymology of Otospongiosis and NaF Therapy"--copy enclosed):

- Ten-year followup of 4,853 surgical and 5,638 medical otospongiotic patients on various NaF treatment regimens.

- Fluoride decreases effectively the amount of trypsin (66 percent of the cases) by increasing antitrypsin activity which expels cytotoxic enzymes and retards sensorineural deterioration.

- NaF therapy can only improve hearing in children; however, it can arrest deterioration of hearing in older patients who have cochlea symptoms.

- NaF action on vestibular function results in less vertigo and tinnitus; also slows down stapedial fixation in some cases.

- Surveillance data which include multiple X-rays of both ear and long bones have not revealed any fluorosis in 10,491 cases surveyed.

- Patient tolerance to therapeutic levels of F- is generally good, particularly if NaF tablets are enteric-coated.

Dental Disease Prevention Activity
Center for Prevention Services

2 Enclosures

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from: New England Journal of Medicine, Vol. 306, No. 8, 2/25/82, pp. 446-459

EFFECT OF THE FLUORIDE/CALCIUM REGIMEN ON VERTEBRAL FRACTURE OCCURRENCE IN POSTMENOPAUSAL OSTEOPOROSIS

Comparison with Conventional Therapy

B. LAWRENCE RIGGS, M.D., EGO SEEMAN, M.D., STEPHEN F. HODGSON, M.D., DONALD R. TAVES, M.D., AND W. MICHAEL O'FALLON, PH.D.

Abstract We assessed the rates of vertebral fracture in patients with postmenopausal osteoporosis. Forty-five patients were not treated (91 person-years of observation); 59 were treated conventionally, with calcium (alone or combined with estrogen) or vitamin D or both (218 years); and 61 were treated with sodium fluoride combined with conventional therapy (251 years). The fracture rate (per thousand person-years) was 834 in untreated patients, 419 in those given calcium with or without vitamin D, 304 in those given fluoride and calcium with or without vitamin D, 181 in those given estrogen and calcium with or without vitamin D, and 53 in those given fluoride, estrogen, and calcium with or without vitamin D. It was reduced in all treatment groups ($P<0.001$ for calcium and $P<1\times10^{-6}$ for other combinations); fluoride (one year of treatment) and estrogen (but not vitamin D) independently reduced the rate from that observed with calcium alone ($P<0.001$). The combination of calcium, fluoride, and estrogen was more effective than any other combination ($P<0.001$). These results provide grounds for optimism about the efficacy of combinations of available agents with sodium fluoride for fracture in postmenopausal osteoporosis. (N Engl J Med. 1982; 306:446-50.)

SODIUM fluoride is a potent stimulator of bone formation; its net effect in patients with osteoporosis is a substantial increase in the bone mass of the axial skeleton.[1-4] Concurrent administration of supplementary calcium with or without vitamin D, however, is required[4,5] to prevent or minimize defective bone mineralization that may occur[6,7] when fluoride is given alone. Because fluoridic bone has increased crystallinity and may have decreased elasticity,[8] the increase in bone mass that occurs after therapy cannot necessarily be equated with an increase in bone strength.

We have evaluated the efficacy of sodium fluoride therapy for postmenopausal osteoporosis by observing the occurrence of vertebral fractures in untreated patients, in patients treated with conventional therapy, and in patients treated with fluoride combined with conventional therapy.

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Supported in part by a research grant (AM-28576) from the National Institute of Arthritis, Metabolism, and Digestive Diseases.

METHODS

Patients

We studied five groups of postmenopausal women during the period 1968 to 1980 (Table 1). Group A consisted of 45 patients who received a placebo (27 patients) or who for some reason had not been treated initially by their attending physicians (18 patients). In Group B, 27 patients received calcium as calcium carbonate (1500 to 2500 mg per day); of these 27, 19 also received vitamin D (50,000 units once or twice weekly). In Group C, 33 patients received both fluoride (50 to 60 mg per day) and oral calcium (800 to 1500 mg per day) (partial data on 24 of these patients were included in a previous report[3]); 13 of these patients also received vitamin D (50,000 units once or twice weekly). In Group D, 32 patients received cyclical conjugated estrogen (0.625 to 2.5 mg per day; mean, 1.3 mg per day) and oral calcium (as calcium carbonate, 1000 to 3000 mg per day); 15 also received vitamin D (50,000 units once or twice weekly). In Group E, 28 patients received fluoride (40 to 60 mg per day), calcium (as calcium carbonate, 1000 to 1500 mg per day), and cyclical conjugated estrogen (0.625 to 2.5 mg per day; mean dose, 1.6 mg per day); 10 of these patients also received vitamin D (50,000 units once or twice weekly). In all therapy groups, patients who did not receive pharmacologic doses were given a daily dose of a multiple-vitamin preparation containing a physiologic dose of 400 units of vitamin D to offset any nutritional deficiency of this vitamin that may have been present before treatment.

All patients were studied prospectively. They were selected from among patients referred to the Metabolic Bone Disease Clinic (Mayo Clinic), according to an identical protocol, and they were followed according to the same protocol. Treatment groups were filled sequentially, and assignment to any of these groups was determined only on the basis of whichever treatment group was then being filled. All patients gave informed consent before enrollment, and essentially all qualified subjects who gave informed consent were included.

Identical criteria for inclusion and exclusion were used for all patients. All were postmenopausal women who had generalized osteopenia and one or more nontraumatic vertebral fractures. None had received previous treatment for osteoporosis, none had any disease known to cause osteoporosis, and none were taking drugs known to affect calcium metabolism. All were ambulatory and willing to cooperate in follow-up. The groups had essentially the same age distributions and the same number of fractures before treatment (Table 1); in Group A the untreated and placebo-treated subgroups were not significantly different in these two features. All patients in the therapy groups were followed up by one of us (B.L.R.) and underwent spinal roentgenography annually.

Laboratory Procedures

In the patients receiving fluoride treatment, fasting serum fluoride was determined by an ion-electrode method after diffusion.[9] Lateral roentgenograms of the thoracic and lumbar spine were obtained at a standard target-to-film distance of 105 cm. Measurements of the vertical height of the anterior (h_a), middle (h_m), and posterior (h_p) regions of the vertebra were made to the nearest millimeter with use of a transparent ruler. With these measurements, fractures were classified into three types: anterior wedge fractures (a decrease in the ratio h_a/h_p); central, biconcave fractures (a decrease in the ratio h_m/h_p); and compression fractures (a decrease in total height, including h_p, as compared with adjacent

vertebras). A fracture was considered to be new if at least one of the three measurements was decreased by 15 per cent or more, as compared with the measurement on the previous roentgenogram. A vertebra was regarded as previously compressed if these measurements were decreased by more than 15 per cent, as compared with the nearest uncompressed vertebra. The error of this method was assessed by comparing measurements made on replicate roentgenograms obtained within a three-month period in seven osteoporotic and three elderly normal women. For paired measurements made of a total of 80 vertebras, the coefficient of variation was 3.2 per cent. In addition, all roentgenograms were examined for evidence of fluoride effect, according to previously described criteria: coarsening and thickening of preexisting trabeculas, appearance of new trabecular structures, and thickening of the end plate.[10] Roentgenograms showing these changes could be consistently separated from roentgenograms made before treatment and from those of the groups not treated with fluoride, when the roentgenograms were read blindly. All measurements were made without knowledge of the group to which the patient was assigned.

Table 1. Characteristics of the Five Study Groups.

GROUP	NO. OF PATIENTS *	PERSON-YEARS OF OBSERVATION	REGIMEN †	AGE		NO. OF FRACTURES BEFORE TREATMENT	
				MEAN	RANGE	MEDIAN	RANGE
A	45	91	Placebo or none	62.9	50–75	5	1–13
B	27 (19)	74	Calcium	65.9	50–81	5	2–13
C	33 (13)	138	Fluoride and calcium	62.9	50–73	5	1–11
D	32 (15)	144	Estrogen and calcium	63.8	52–79	6	2–14
E	28 (10)	113	Fluoride, calcium, and estrogen	62.9	47–71	4	1–9

*Figures in parentheses denote numbers of patients who also received vitamin D.
†Calcium was given as calcium carbonate.

Statistical Analysis

In comparing fracture rates, expressed per thousand person-years of observation, we assumed that the numbers of fractures during the period of observation followed a Poisson distribution. We tested the hypothesis that two fracture rates from two independent samples were equal, using the simple approximate tests for Poisson variates as decribed by Cox.[11] Of necessity, multiple comparisons of fracture rates were made with use of the same groups (or subsets of the same groups) and Bonferroni's inequality method was used to control the corresponding P value.[12] Thus, because approximately 20 tests were conducted, P values were considered significant at the level of $\leq 0.05/20$, or ≤ 0.0025.

Results

Twenty-three of the fluoride-treated patients (Groups C and E) had adverse reactions (38 per cent), which caused five of them to discontinue therapy; 13 had rheumatic symptoms (joint pain and swelling or painful plantar fascial syndrome), nine had gastrointestinal symptoms (severe nausea and vomiting, peptic ulcer, or blood-loss anemia), and one had both rheumatic and gastrointestinal symptoms. These reactions were not observed in the untreated patients (Group A) or the conventionally treated patients (Groups B and D). In 14 of these patients (24 per cent), vitamin D was discontinued or the dose was reduced because of hypercalcemia (serum calcium >10.1 mg per deciliter [2.5 mmol per liter] in 10 patients) or hypercalciuria (urinary calcium >350 mg [9 mmol] per day in four patients). Eight patients (13 per cent) among the 60 taking estrogen (Groups D and E) required hysterectomy or uterine dilation and curettage because of menorrhagia or metrorrhagia. None, however, had endometrial carcinoma or vascular thrombotic events.

Figure 1 shows the vertebral fracture rates (per thousand patient-years of observation) in the five groups: Group A, 834; Group B, 419; Group C, 304; Group D, 181; and Group E, 53. Because of the likelihood that at least one year of treatment would be required for fluoride to increase bone mass substantially, we also determined fracture rates in the therapy groups after excluding the data for the first year of therapy. These rates were 532 in Group B, 210 in Group C, 205 in Group D, and 35 in Group E (Fig. 1). The differences between the untreated group and the treated groups were significant ($P<0.001$ for the patients in Group B, who received calcium with or without vitamin D, and $P<1\times10^{-6}$ for those in Groups C, D, and E, who also received fluoride or estrogen or both).

We next compared fracture rates in patients who received only calcium with or without vitamin D (Group B) and those who received calcium with or without vitamin D plus the variable components of fluoride, estrogen, or both (Groups C, D, and E) (Table 2). Patients in Groups C and E, all of whom received fluoride, had a marginally lower fracture rate (191) than did those in Groups B and D, who did not receive fluoride (261), but the difference was not significant ($P = 0.055$), especially in view of the multiple tests. When the data for the first year of therapy were excluded, however, the corresponding rates were 132 and 302, which were significantly different ($P<0.001$). Patients in Groups D and E, all of whom received estrogen, had a significantly lower fracture

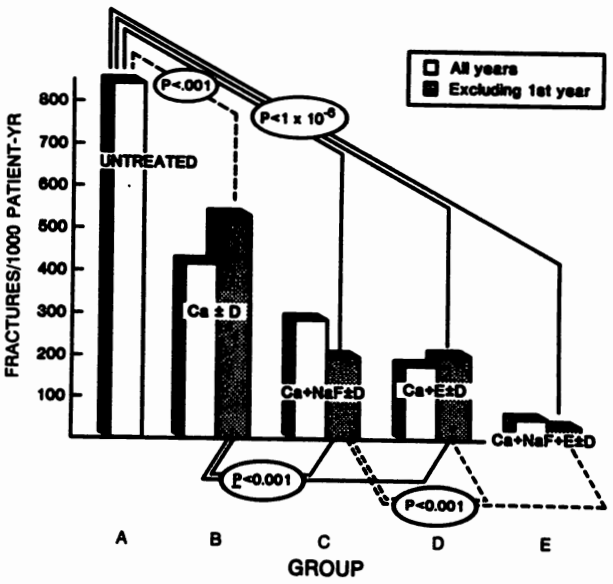

Figure 1. Comparison of Fracture Incidence in Untreated Patients and Patients Receiving Various Combinations of Calcium (Ca), Sodium Fluoride (NaF), Estrogen (E), and Vitamin D (D).

The fracture rate was reduced in all treatment groups. The components of fluoride (after one year of treatment) and estrogen independently reduced the fracture rate from that observed with calcium alone, and a combination of all three agents was maximally effective.

Table 2. Effect of Fluoride and Estrogen (Together or Alone) on Fracture Rates in the Treatment Groups.*

DATA FOR ENTIRE STUDY PERIOD

		Fluoride: Yes		Fluoride: No	
		fracture rate/1000 person-yr (group)			
Estrogen	Yes	53 (E)		181 (D)	125 (D + E) [P<0.001]
	No	304 (C)		419 (B)	344 (B + C)
		191 (C + E)	[P = 0.055]	261 (B + D)	224 (B + C + D + E)

DATA EXCLUDING THE FIRST YEAR

		Fluoride: Yes		Fluoride: No	
		fracture rate/1000 person-yr (group)			
Estrogen	Yes	35 (E)		205 (D)	132 (D + E) [P<0.001]
	No	210 (C)		532 (B)	309 (B + C)
		132 (C + E)	[P<0.001]	302 (B + D)	209 (B + C + D + E)

*The treatments in each group are given in Table 1. All patients also received calcium.

rate (125) than did those in Groups B and C, who did not receive estrogen (344) (P<0.001). The fracture rate in patients given both fluoride and estrogen (Group E) was significantly lower (P<0.001) than that in those given fluoride (Group C) or estrogen (Group D) alone (or with vitamin D) as the major therapy. Furthermore, fluoride and estrogen acted independently, with only a slight indication of a synergistic interaction. When therapy was evaluated after only one year of treatment, the fluoride and the estrogen components were found to be equally effective and the concurrent use of fluoride and estrogen was maximally effective. The addition of vitamin D was found to have reduced the incidence of vertebral fractures marginally (from 227 to 129; P<0.05) when the groups receiving fluoride (C and E) were combined. In the other groups or in combinations of groups, however, we were unable to demonstrate a significant effect due to vitamin D (Fig. 2).

Sixty per cent of the patients treated with sodium fluoride had radiographically apparent increases in vertebral bone mass that could be consistently differentiated when the roentgenograms were read blindly. Patients with these changes had only approximately one seventh the fracture rate of the rest of the patients. The number of vertebral fractures before treatment, the mean dose of fluoride, the mean levels of serum fluoride, and the mean duration of treatment did not differ significantly between the patients responding and those not responding (Table 3).

DISCUSSION

Because the morbid event of spinal osteoporosis is vertebral fracture, the most important criterion for

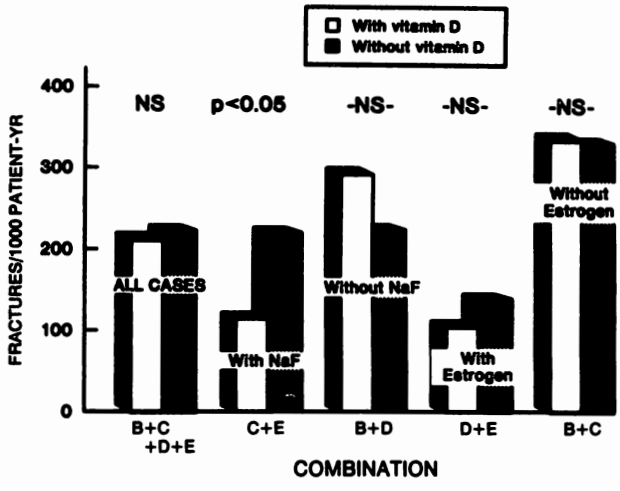

Figure 2. Comparison of Fracture Rates after Various Combinations of Therapy with and without Vitamin D.

Except in the groups receiving sodium fluoride, in whom the addition of vitamin D marginally reduced the incidence of fractures, no significant (NS) effect of vitamin D could be demonstrated.

successful treatment is reduction of the vertebral fracture rate. In the present study we wished to place in perspective the value of fluoride therapy for postmenopausal osteoporosis by examining the rate of fracture occurrence in untreated, conventionally treated, and fluoride-treated patients. The patients in all therapy groups were chosen according to identical criteria and were studied prospectively. For untreated patients, fracture rates were derived prospectively in some and retrospectively in others. The groups were comparable in age and number of vertebral fractures at entry. Thus, although the patients were not randomly assigned, we believe that the groups were sufficiently matched to allow us to assess group differences in fracture rates.

We found that treatment with calcium — alone or combined with estrogen, vitamin D, or both — reduced the vertebral fracture rate to half (or less) of the rate observed in untreated patients. This significant reduction probably resulted from the ability of these agents to arrest or retard the rate of bone loss[13,14] or — in estrogen therapy — to increase bone mass minimally.[15] Their inability to increase bone mass substantially probably accounted for their inability to reduce the fracture rate more dramatically.

The effect of fluoride therapy on the fracture rate in patients with postmenopausal osteoporosis has not been systematically studied before. We found that the fracture rate in the group receiving fluoride and calcium (with or without vitamin D) — Group C — was 30 per cent lower than that of the group receiving calcium (with or without vitamin D) — Group B. It appears, however, that a more pronounced therapeutic

effect of fluoride therapy was obscured by two confounding variables. The first was the time necessary for fluoride therapy to increase vertebral bone mass. Harrison et al. found that one year of treatment was required to increase axial bone mass substantially, as assessed by regional neutron-activation analysis.[15] On reanalysis after exclusion of the data for the first year of therapy, the rate of vertebral fracture was 61 per cent lower. The second variable was the individual variation in responsiveness. Briancon and Meunier found that treatment for two years doubled the mean values for trabecular bone volume in iliac-crest biopsy samples; however, one fourth of the samples showed no increase.[5] Furthermore, we found that 60 per cent of fluoride-treated patients had a radiographically evident increase in vertebral bone mass, and these patients had approximately one seventh the fracture rate of the other patients. This finding suggests that a critical threshold level for vertebral bone mass must be achieved by fluoride therapy before the fracture rate is reduced below that occurring after conventional therapy. In responding patients, attainment of this level necessitated at least one year of therapy; in the remainder, it was still not reached after four to six years of therapy.

Why a substantial minority of our patients did not respond to therapy is unclear. Our studies suggest that differences in responsiveness cannot be explained by variations in the severity of the osteoporosis, in fluoride dosage, or in fluoride bioavailability. Instead, we hypothesize that an intrinsic abnormality of osteoblast function is present in some patients with osteoporosis and prevents stimulation of bone formation to a level much above basal levels. Studies of iliac-crest biopsy samples by histomorphometry have disclosed a subgroup of patients (who received no treatment) with a decrease in the indexes of bone formation.[16,17] Thus, sodium fluoride therapy may have served as a probe to identify more definitively an important subgroup of patients in whom impaired osteoblastic activity contributed to pathogenesis.

Therapy was most efficacious in the group receiving fluoride, calcium, and estrogen (Group E). This finding agrees with that of Harrison et al., who reported that four patients treated for three years with fluoride and estrogen had a greater increase in axial bone mass (15.6 per cent) than did four patients treated for three years with fluoride alone (9.6 per cent).[15] Because fluoride is a potent stimulator of bone formation and estrogen is a potent inhibitor of bone resorption, an additive effect by these two agents was expected. However, estrogen has important adverse effects, including menometrorrhagia and induction of endometrial carcinoma.[18] Whether the efficacy of the estrogen component of combined therapy compensates for its side effects is problematic.

Table 3. Characteristics of Subgroups with or without Increased Vertebral Bone Mass during Fluoride Therapy.*

CHARACTERISTIC	SUBGROUP	
	INCREASE IN MASS	NO INCREASE IN MASS
No. of patients (per cent)	33 (60)	22 (40)
Vertebral fracture rate (per 1000 person-yr)		
Entire study period	56 †	356
Study period excluding 1st yr	30 †	253
Median no. of fractures before treatment	4	4
Mean dose of fluoride (mg/day) [±S.E.]	56.7±1.7	57.2±1.5
Mean serum fluoride (μmol/liter) [±S.E.]	7.8±0.4	7.7±0.6
Mean duration of treatment (yr)	4.3	4.6

*Table includes only patients who completed four years of therapy — i.e., 55 of the 61 given fluoride.

†Significantly different from value for subgroup without increased bone mass ($P<0.001$).

Moreover, the addition of vitamin D to the therapeutic regimens containing fluoride either failed to reduce the fracture rate or reduced it marginally. The use of vitamin D was also associated with a substantial incidence of hypercalcemia or hypercalciuria or both. Thus, we believe that vitamin D should not be included as a component of therapy.

In conclusion, our results provide grounds for optimism about the efficacy of combinations of available agents with sodium fluoride in the prevention of fractures in postmenopausal osteoporosis. For patients who do not fully respond it is important to obtain a better definition of the causal mechanisms, time course, and extent of the limited response. Such information may lead to a program of fluoride therapy that is even more effective in preventing fractures.

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AMERICAN JOURNAL OF OTOLOGY/VOLUME 1, NUMBER 4 *April 1980*

ENZYMOLOGY OF OTOSPONGIOSIS AND NaF THERAPY

Jean R. Causse, M.D., George E. Shambaugh, M.D.,† J. Bernard Causse, M.D.†† and Paul Bretlau, M.D.§*

The innermost mechanism of the otosclerotic disease has remained unknown for a long time, even when stapedectomies began to give good functional results in stapedial otosclerosis.

Numerous authors tried, for many years, to discover this process, but opinions are still divided. Toxic factors causing damage to the peripheral cochlear neuron and more recently vascular "shunts" have been proposed. Extensive otosclerotic bone transformations breaking the cochlear endosteum and causing distortion of the contours of the cochlea were demonstrated by Schuknecht.[1,2,3] Alterations of the spiral ligament were shown by Linthicum.[4,4,] A good review of the history was recently done.[7] However, these lesions seem less frequent than the numerous cases of progressive cochlear deterioration in stapedial otosclerosis (about 75 percent of the cases, operated on or not) and in capsular otosclerosis.

The authors' postulate on a possible enzymatic cause began in 1961 on the constatation of lysosomes between the mitochondries in mononuclear histiocytes in the otospongiotic microfoci (Fig. 1). A close and profitable collaboration between Georges Chevance (biochemist in Paris), Martin Jorgensen and Paul Bretlau (anatomopathologists in Copenhagen), José Uriel and Josette Berges (enzymologists in Paris), and two otologic surgeons George Shambaugh (Chicago) and Jean Causse (Béziers), led us to an enzymatic concept of otospongiosis, which fits perfectly with the various clinical pictures of the disease. This concept, established on numerous anatomopathologic findings and enzymatic examinations and experiments, was confirmed recently and completed by the cochlear pathology found in capsular microdissection by Jonhsson, Hawkins, and Linthicum, who have remarkably schematized the characteristic pattern of the expansion of the foci and their relation to the audiometric findings.[7] Both biochemical and vascular factors seem responsible for the sensorineural hearing loss associated with otospongiotic and/or otosclerotic lesions, depending upon the case. Our enzymatic concept is complementary to Linthicum's theory, in which vascular shunts could cause hyposia and thus rob the spiral ligament of the necessary oxygen, leading to the results of anoxia. Those are hyalinization, calcification, and ossification.[4,5,6]

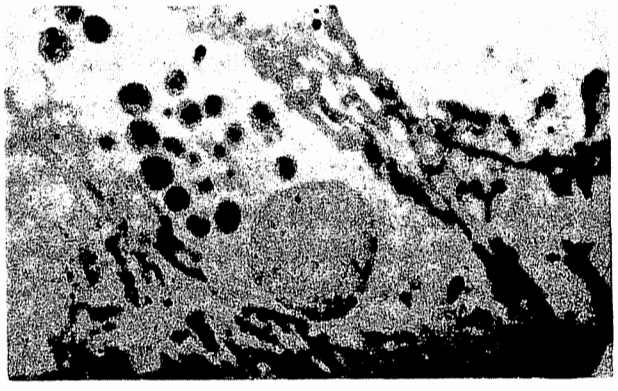

Figure 1. Lysosomes between mitochondries in histiocytes.

The starting point of our research was the discovery of osteoid lamellae, which led us to an intensive electron microscopic study of otospongiotic foci by avoiding decalcification artefacts and thus permitting more exact cellular study.[8,9]

These findings, obtained from middle ear surgery, have shown that the otospongiotic foci are made by the confluence of microfoci, which finally coalesce and in which destruction areas and pseudohaversian bone rebuilding areas coexist, intricated in the same section. In close vicinity to these otospongiotic microfoci are lysis areas, lined by collagen fibrils in process of destruction, losing their normal striation and resulting in a very special "pipette Pasteur" aspect.

By electron microscopy, we found that cells actively engaged in the lysis process, which characterizes the initial typical phase of otospongiosis, are histiocytes, always numerous and constant in the

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lysis areas.[10] Osteoclasts, previously considered responsible for lysis as first shown by Siebenmann, are very rare in active foci; they are generally abundant in the center of the otospongiotic lesions (Fig.2).[12,13]

The cytoplasm of these histiocytes shows lysosomes containing a great number of hydrolytic enzymes. Increase of oxygen stimulates lysosomal activity and causes membrane rupture, resulting in intracellular destruction (intrusion) and extracellular enzymes spreading (extrusion) (Fig. 3).

The presence of histiocytes containing lysosomes in the otospongiotic microfoci, and of collagen fibrils in process of destruction on the borders of these microfoci, led us to suspect an enzymatic action. In fact, this intense hydrolytic activity was confirmed by the demonstration of an important phosphatasic acid activity in the cells inside the microfoci and in the front of the foci (Fig. 4).[14]

ENZYMATIC RESEARCH

Our investigations are based upon more than 3400 perilymph samples taken during stapedectomies.

The first period of experimentation dealt with a screening method, derived from the Adams' technique and based upon the intensity of digestion of the gelatin of photographic films by a drop of perilymph under certain conditions, in a water-saturated sterilizer at 37 °C in order to avoid dessication.[15] Statistical correlations established between the intensity of the proteolytic action of the perilymph and the cochlear deterioration expressed in B.C. studied for one or two years have shown (1) for direct correlations, 84 percent of cochlear deterioration in cases rich in hydrolases and, (2) for inverse correlations, only 16 percent of progression toward sensorineural hearing loss in cases without notable proteasic activity. [16,17]

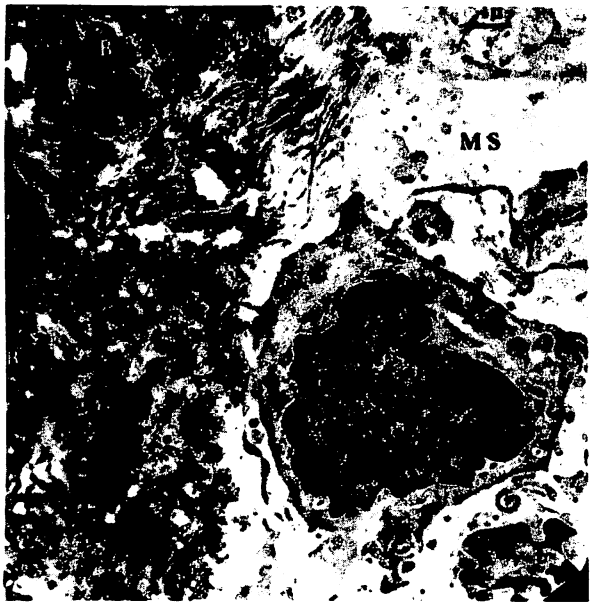


Figure 2. Mononuclear histiocytes.

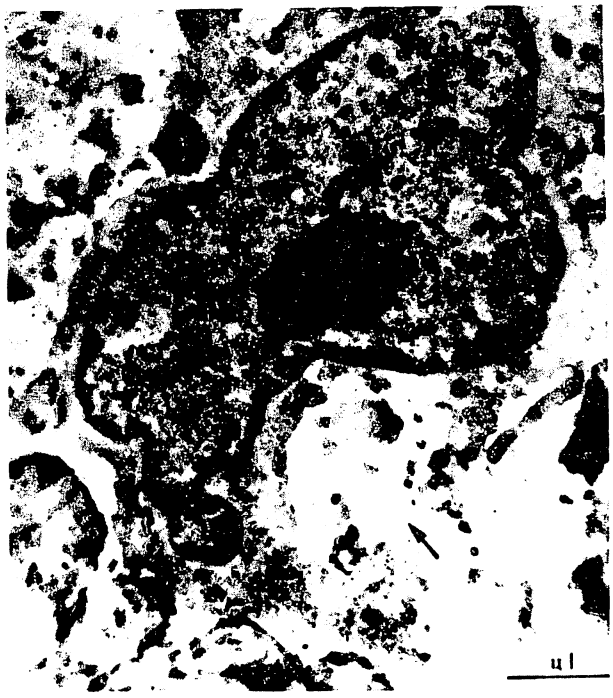


Figure 3. Extracellular enzymes spreading.

In a second period, a qualitative study of perilymph enzymes by means of microelectrophoresis technique allowed us to find six enzymes (phosphatasic acid, alphachymotrypsin, collagenase, ribonuclease, lactate dehydrogenase, and trypsin).[18] Six others were not found (elastase, desoxyribonuclease, carboxypeptidase, cathepsin, hyaluronidase and galactosidase).[19]

The third step proceeded with quantitative study by specific microdosages. The dosage of trypsin was done according to the Erlanger, Kokowsky, and Cohen method, using the characteristics of the enzyme chromogenic substrate.[20] The dosage of alpha 1 antitrypsin was formulated by radial immunodiffusion in agarose (Mancini's method).

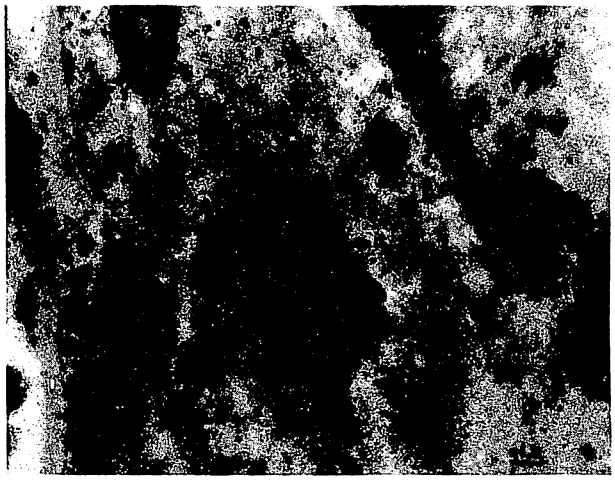


Figure 4. Phosphatasic acid activity.

For perilymph tryptic activity, the results of correlations between this tryptic activity and cochlear deterioration demonstrated that for a minimum quantity of 2 to 4.5 microg/ml, there are only 20.08 percent of progressive cases, whereas this proportion reaches 100 percent when the amount of trypsin appears to be maximal; i.e., about 10 microg/ml.

For perilymph antitryptic activity, the same correlations established in parallel demonstrated that for alpha 1 antitrypsin concentrations of 0.043 to 0.029 microg/ml, 97 percent of patients do not progress toward cochlear deafness. On the contrary, if the alpha 1 antitrypsin values are lower than 0.026 microg/ml, the proportion of cochlear deterioration is suddenly reversed and reaches 91 percent.[21]

The comparison of results obtained by measurement of tryptic and antitryptic activity shows a sudden reversal of progression of tryptic activity at about 4.6 microg/ml, and of antitrypsin activity at about 0.026 microg/ml. It may be deduced that when the balance trypsin-antitrypsin is upset, cochlear deterioration occurs. Thus it seems that the mechanism of cochlear otospongiosis has an enzymatic origin and is more precisely caused by the disruption of the normal enzymatic balance.[21]

The highly diffusive hydrolytic enzymes and the relative metabolic isolation of the otic capsule explain the possibility of the rupture of this equilibrium, and thus the tryptic toxic action on the hair cells and the mechanism of the bony rebuilding of the niche.

Uriel and Berges and the authors are now trying to find the exact correlations between the disruption of the trypsin-antitrypsin balance and the values of other enzymes, particularly alpha 2 macroglobulin and the cathepsin B, and their connection with audiometric findings. The problem is complex, and although some progress has been made it is not yet totally solved.

EXPERIMENTAL RESEARCH ON ANIMALS

To be able to confirm these enzymatic findings, Chevance began an experimental study on animals.

First, in collaboration with Manach and Adrian in the Pasteur Institute in Paris (1975), he conducted experimental investigations on guinea pigs using intracochlear perfusions of various solutions of trypsin with the usual precautions.[22] With a perfusion of a solution of trypsin at 0.2 percent, the cilia lose their normal characteristic straightness and become bowed or even bent down, looking like a cornfield after a storm. In proportion, as the contact time increases, the lesions become aggravated, and some cilia appear partially cut at their base, others even completely disappear. On the contrary, the lowest concentration of trypsin solution at 0.01 percent only attack the external row of these outer hair cells (Fig. 5).

Of course, the experimentation on animals was a short-term investigation, using concentrations of trypsin about 200 times greater than those of trypsin in the perilymph, but it constitutes proof of the nocivity of the trypsin action on the external hair cells and of its proportional attack according to the doses and the time.

Figure 5. Hair cells bowed by enzymatic activity.

Secondly, Chevance, with the collaboration of Niaussat in the Animal Acoustic Laboratory (INRA) of Professor Busnel, carried out the study of an experimental pattern of otospongiosis on laboratory animals.[23] The depositing of various doses of trypsin crystals at the anterior part of the oval niche causes an increase of tryptic activity of the perilymph from 2.5 to 4 microg/ml in 72 hours and an important hearing loss owing to cochlear deterioration and bony remodelling of the niche from the 20th to the 90th day.

These findings are identical to those in otospongiotic patients. Moreover, the hair cell alterations confirm findings encountered in cochlear perfusions, chiefly the more important action of trypsin and the predominance of the lesions on the external row of the outer hair cells, and the transformation of mitochondrial structures in the hair cells themselves. Last of all, the histologic finding of contralateral sensorineural deterioration by acting on only one ear without any bony alteration of the contralateral niche gives a new impetus to the problem of crossing fibers through the superior olivary nucleus, the central nucleus of the lateral lemniscus, and the inferior colliculus. Studies should be carried on in this direction, but the current findings seem to confirm the theory of cochlear interdependence. This could be very important for the explanation of the bilateral perceptive hearing loss in audiometric bilateral cochlear otospongiosis with a conductive component on only one ear, as seen very often in otosclerosis surgery.

ENZYMATIC CONCEPT OF OTOSPONGIOSIS

All this data was the basis of the authors' enzymatic concept of the otospongiotic disease, which fits perfectly with the disease's various particularities—the stimulus given to otospongiosis by (1) pregnancy, which releases enormous quantities of

estrogens, causing fragility of the lysosomal membranes and thus the bursting of the lysosomes and the spreading of ther enzymes, and by (2) estrogens drugs, for instance contraceptive pills. [16,17,24-29]

The otospongiotic process generally starts in the area of numerous cartilaginous remnants scattered through the enchondral layer of the otic capsule. Hydrolytic enzymes and resultant proteases of cellular destruction can spread from the focus of the lateral wall and from the other foci included in the otic capsule into different parts of the cochlea.

When the enzymes only cause a bony rebuilding owing to the second pseudohaversian phase following the primary lytic process of destruction, a conductive deafness occurs because of stapedial fixation (Fig. 6).

When the enzymes spread into the labyrinthine fluids either by splashing through the canaliculi, or by diffusion, according to the authors' enzymatic concept and to Linthicum, Johnsson, and Hawkins' pattern of expansion of active focus, they lead to a perceptive hearing loss. However, if the foci are very small and less active, the disease may remain histologic and undiscovered.

Vestibular impairment is less frequent, because in most cases the otospongiotic foci are not localized in the vestibular portion of the otic capsule. But the spreading of enzymes into the labyrinthine fluids very often cause an irritative-type tracing of high frequency and low amplitude in the ENG recording of the torsion swing test, performed systematically on otosclerotic patients, even in the absence of any clinical manifestation of vertigo or dizziness.[16-,24-33] Of course, all these types may be mixed, giving various aspects of the disease.

A double consequence results from the enzymatic concept. First, there is a possibility of therapy using an enzymogenesis regulator to stop or to slow down the activity of the otospongiotic microfoci and thus arrest the cochlear deterioration, and, in a smaller proportion, the stapedial fixation. Second, there is early detection of the cochlear deterioration thanks to systemtic audiometric check-ups in patients previously operated on. Stapedial fixation must be detected in the descendants of these patients owing to systematic audiometric investigations including the elicitation of the stapedius reflex to check on a possible on-off effect, typical of the onset of the stapedial fixation.

Figure 6. Focus of the lateral wall with stapedial fixation.

BASIS OF IMMEDIATE POSTOPERATIVE THERAPY

Immediate postoperative therapy is easy to justify based on the following factors.

Changes in perilymph pressure and operative trauma, even if slight, cause hair cells to suffer from a shortage of oxygen and glycogen (these may affect any sensorial cell in the body as well). Decreasing perilymphatic oxygen tension causes tinnitus and cochlear drop in the area of the cochlea. Dizziness or vertigos are the labyrinthine reaction to this defect. Moreover, surgical microtrauma, enhanced by intraoperative bleeding, has a side effect on the vascular supply to the cochlea: capillary dilatation and increased permeability. The escape of serum from the capillaries and the toxic action of serotonins from the platelets induce hydrops within the labyrinth, whereas sludging of red cells within the capillaries slows the circulation and promotes anoxia with further capillary damage and temporary or permanent hair cell trouble. Noise exposure during the early postoperative period increases oxygen consumption of hair cells and is especially harmful at this time.[34] The only means to combat the shortage of perilymph oxygen and glycogen is to bring oxygen to the hair cells through the stria vascularis by increasing the intralabyrinthine blood flow and glycogen by intravenous injections of glucose hypertonic solution.

Labyrinth blood supply is given by the internal auditory artery, which is an end artery originating in the vertebro basilar artery through the posterior cerebellar artery. Thus, cochlear blood flow consists of 90 percent vertebral artery blood and 10 percent carotid artery blood; i.e., its origin is mainly vertebral and consequently of peripheral value.

Cochlea and posterior labyrinth are contained in the same bony shell, supplied by the same internal auditory artery, and bathed in the same fluids. Consequently, vasoactive drugs acting on this posterior labyrinth, for instance those used in Meniere's disease, must act efficiently on the cochlea. Moreover, the menbraneous structures are almost similar but have peculiar responses: hearing loss and tinnitus for the cochlea, vertigos for the posterior labyrinth.

Perilymph production derives mainly from the cochlear blood flow. The perilymph has two main sources: (1) the influx of cerebrospinal fluid both through the cochlear aqueduct and through the modiolar spaces, and (2) local endocochlear production originating from the inner ear blood flow. However, the major source is the cochlear blood flow, with a predominance of 78 percent.[35] The cochlear blood flow depends on the arterial blood supply through the large cervical arteries, as experienced by the authors.

The early postoperative period is critical in any stapedectomy, requiring daily bone-conduction audiograms and Weber tests from the first postoperative day to detect a possible cochlear drop immediately. This condition is prerequisite in order to obtain an effective action of vasoactive drugs, which generally become inactive 36 hours after the cochlear drop. The drop in cochlear response is evidenced by a decline in both conduction levels, a shift of pure tone and speech Weber tests to the better ear (operated on or not) and a distortion with impaired discrimination in speech audiometry. Tinnitus and vertigo are very often absent at this early period, one should never wait for these to appear. Deferring the first audiogram to the third or fourth week after stapedectomy eliminates any possibility of reversing cochlear disorders.

Drugs that improve cochlear blood flow and thus afford oxygen and glycogen to the hair cells and combat the labyrinthine reaction are as follows:

VASODILATORS. The first vasodilator used is the old nicotinic acid, always by repeated intravenous injections given intermittently three to five times a day, and never by continuous perfusions. This method "massages" the impaired intralabyrinthine circulation, brings oxygen to the hair cells through the stria vascularis, and promotes recovery of cochlear function. It should begin 36 hours after the operation (to avoid increased postoperative bleeding) and should continue according to the case.

The second vasoactive drug is Papaverine, which has earned the universal approval of clinicians and researchers. It increases cochlear blood flow considerably and decreases the systemic blood pressure only slightly. Moreover, it relaxes smooth muscles of large blood vessels, particularly during vagospasm. Its effects are relatively long lasting. Papaverine appears to be the drug of choice.

The third vasodilator is histamine (and betahistine) given by progressive intravenous dilute dosage, as in Meniere's disease. Many authors, chiefly Shambaugh, are convinced that this method is the best, but its action on the blood flow of the cochlea and of the brain is too often neutralized by a fall in arterial blood pressure.

INHALATIONS OF 10 PERCENT CARBON DIOXYDE AND 90 PERCENT OXYGEN. These increase cochlear blood flow with little change in systemic blood pressure as demonstrated by Lipscomb.[36,37] Candin recommends these inhalations to combat hair cell anoxia.[38] Shambaugh and Shea are using 5 percent CO_2 and 95 percent 0_2 at 6 liters/minute for five minutes every hour for the first three postoperative days.

ADDITIONAL THERAPY. This includes very small doses of heparin sodium (2500 units) by subcutaneous injection two or three times daily after the third postoperative day (not before, to avoid increased bleeding in the middle ear). At these very small doses, heparin helps vasodilator action, tends to resorb exudates, and prevents phlebitis.

Steroids, added to usual antibiotics, are helpful because of their antiinflammatory effect on the middle ear and tubal function.

Hypertonic glucose solution 20 cc is given three times a day by intravenous injections in case of cochlear drop, dizziness, or tinnitus. It increases cochlear blood flow and brings glycogen and oxygen to hair cells.

Hydrocortison hemisuccinate is the newest drug used. Given by intravenous injection of 500 mgr three times a day, it reduces the edema of the hair cells and helps vasodilators and hypertonic glucose solution. Thus it combats cochlear drops with effectiveness, on the condition that this set of three drugs is administered as soon as possible before the 36th hour of the drop.

MAINTENANCE THERAPY

Maintenance therapy acts on the frequent progres-sive cochlear otospongiotic impairment and consists particularly of sodium fluoride therapy, originated by Shambaugh.[31,32,34,39,40,41,42]

The mechanism of NaF therapy is an enzymatic action on the first phase of destruction, the most important in regard to the bony foci and inner ear fluids. NaF seems to increase the antitrypsin activity through alpha 2 macroglobulins and thus to balance tryptic activity, which has a toxic action on the hair cells and destroys the collagen fibrils of the bony otic capsule, particularly in the niche and in the stapedial area.

The effect of fluoride medication is twofold. An early effect of fluorides is their efficiency in the microfoci, expelling the cytotoxic enzymes into the labyrinthine fluids, and in retarding or arresting the sensorineural deterioration in otospongiosis. A less evident, more gradual and long-term effect is in reducing the bone-remodelling activity of the focus. Both are of enzymatic origin.

Objective evidence of the favorable effect of fluorides on otospongiotic foci is afforded by (1) repeated polytomographic studies, (2) extensive statistical analysis of large numbers of treated and untreated patients (there is computerized data on 10,441 cases with long-term results on operated or unoperated otospongiotic patients over a 10-year-period with various NaF doses), and (3) comparative dosages of trypsin concentration in perilymph before and after NaF therapy.[43,44] In this study, the results clearly show that the trypsin amount significantly decreases in about 66 percent of cases with moderate doses of NaF, generally 45 mg a day, the results having been corrected in relation to control series.

Optimal dosage is determined by the concept that the effect of NaF is based on presence more than on weight (as any enzymogenesis regulator). We must reach an action threshold, below which it does not act and beyond which its activity does not increase in

relation to the doses. Clinical trials with various doses from 3 to 60 mgr daily led the authors to the notion that (1) very small doses ranging from 3 mg to 6 mg daily are sufficient to act on pure cochlear otospongiosis (less active than the stapedial fixation from the enzymatic point of view), and (2) on the contrary, doses must be greater, ranging from 15 mg to 45 mg daily for stapedial fixations with a cochlear component in which an important enzymatic activity is needed to cause both bone rebuilding of the niche and spreading of hydrolytic enzymes into the labyrinthine fluids. Larger doses of 60 mg to 120 mg daily did not appear to give any better results, because NaF has a double action according to the doses.[45] NaF doses of 60 mg daily or more cause a pseudohaversian rebuilding resulting in the formation of a very fragile new bone, whereas doses of 45 mg daily or less do not increase bone formation and act only on enzymatic activity. For this reason, we always give our patients moderate doses of NaF, ranging from 15 mg to 45 mg daily, to stop cochlear deterioration without increasing stapedial fixation. Thus we generally do not need vitamin D and calcium supplements to prevent formation of abnormal bone.

Based on this data, the authors usually prescribe:

For Adults

60 mg daily, five days a week, only for advanced otospongiosis with a very active cochlear component, and for the cases in which less important doses have not acted; and always for a very short period of time, 6 to 8 months at the very most.

45 mg daily, continued for two years, as a starting postoperative treatment for all surgical cases with a progressive cochlear component.

30 mg daily; for two years also, as a maintenance dose following the previous one, if the yearly audiometric surveillance shows a good stability of bone conduction levels.

15 mg daily, as a lasting dose for years, until inactivation of the otospongiotic foci is proved by bone conduction stability for two to four years.

3 mg to 6 mg daily, continued for years, for pure cochlear otospongiosis as well as preoperative therapy for stapedial otospongiosis with an important progressive cochlear deterioration.

For Children

The authors give much more moderate doses than for adults, ranging from 1.5 mg to 10 mg daily, to avoid possible stunting of the growth by a too early calcification of the long bone matrix.

Surveillance

Surveillance of lasting NaF therapy must be three-fold: (1) audiometric checkup once a year in order to determine the stability or the progression of the bone conduction levels, (2) polytomography x-ray investigation to verify NaF's action on the bony otic capsule every year, and (3) x-ray investigations of the long bones, lumbar column, and pelvis every two years to detect possible fluorosis.

There is no toxicity at these moderate doses, chiefly if we consider that part of NaF is destroyed in the digestive tract by tricalcic phosphate and calcium carbonate. Doses prescribed are below the therapeutic security levels and thus far below toxic doses. Furthermore, the authors have never seen any fluorosis on more than 10,000 cases surveyed by computer.

Tolerance

Tolerance is generally good and gastric intolerance is very rare if NaF is prescribed in enteric-coated tablets. This is the only means to avoid NaF dissociation by gastric acids, resulting in production of very harmful hydrofluoric acid provoking severe gastric troubles and in suppression of NaF activity. Care must be taken in patients suffering from chronic nephritis, as impaired excretion of NaF might lead to toxic concentrations in the blood. On the contrary, the moderate doses are compatible with cardiovascular diseases, for the sodium doses correspond to 8.20 mg per 15 mg NaF enteric-coated capsule; that is, 24.60 mg for 45 mg NaF daily. Lactose generally used as an excipient must be avoided for patients suffering from diabetes.

RESULTS

The functional results yielded by our computerized data on 10,441 cases with a follow-up ranging from three months to ten years are favorable.

However, favorable results only means arrest of cochlear deterioration in cases having a progressive cochlear component, because NaF acts only as a stabilization factor, and thus it cannot improve hearing, except in children. Moreover, a follow-up of one or two years at least is indispensable to a sure approach to the problem, because the otospongiotic disease generally develops by progressive steps, separated by inactive periods owing to spontaneous balance enzyme-antienzyme activity. For this reason, the authors have always corrected the functional results in relation to equivalent control series, taking into account the 25 percent spontaneously nonprogressive otospongiosis, operated or unoperated.

The main computerized data is summarized in Table 1 and Figure 7. Table 1 shows higher doses in surgical cases than in medical ones, as already reported. Figure 7 proves that the various doses have been correctly established to pass slightly over NaF action threshold, since percentages in relation to different doses related to enzymatic activity are similar for medical cases and surgical ones; i.e., 66.41 percent for medical cases and 67.52 percent for surgical cases.

As for its action on stapedial fixation, NaF

TABLE 1. NaF STATISTICAL DATA ON 10,491 CASES (DECEMBER 1978)

SURGICAL CASES	
NaF 3 mg to 6 mg	661
NaF 15 mg	856
NaF 30 mg	680
NaF 45 mg	2,606
NaF 60 mg	50
Total of Surgical Cases	*4,853*
MEDICAL CASES	
NaF 3 mg to 6 mg	3,365
NaF 15 mg	1,563
NaF 30 mg	37
NaF 45 mg	673
Total of Medical Cases	*5,638*
TOTAL OF SURGICAL AND MEDICAL CASES	*10,491*

seems to slow it in some cases, but this is very difficult to evaluate. It is obvious that NaF action cannot release stapedial fixation, for moderate doses of 45 mg or less act only on the first otospongiotic phase of lysis and thus only prevent the second phase of pseudohaversian rebuilding. Larger doses increase the stapedial fixation, as already related.

Fluoride action on vestibular function is evident. Patients generally show less vertigo or dizziness after some months of NaF therapy, as well as less tinnitus for cochlear function. Moreover, the authors experienced a series of 224 comparative studies by means of torsion swing test ENG recordings before and after NaF therapy on operated or unoperated otospongiotic patients. The more or less irritative type tracing, usual in otospongiotic patients, tends to become less irritative or even normal in almost 70 percent of operated ears and 60 percent of unoperated ears in relation to the control series after six months or more of NaF therapy.

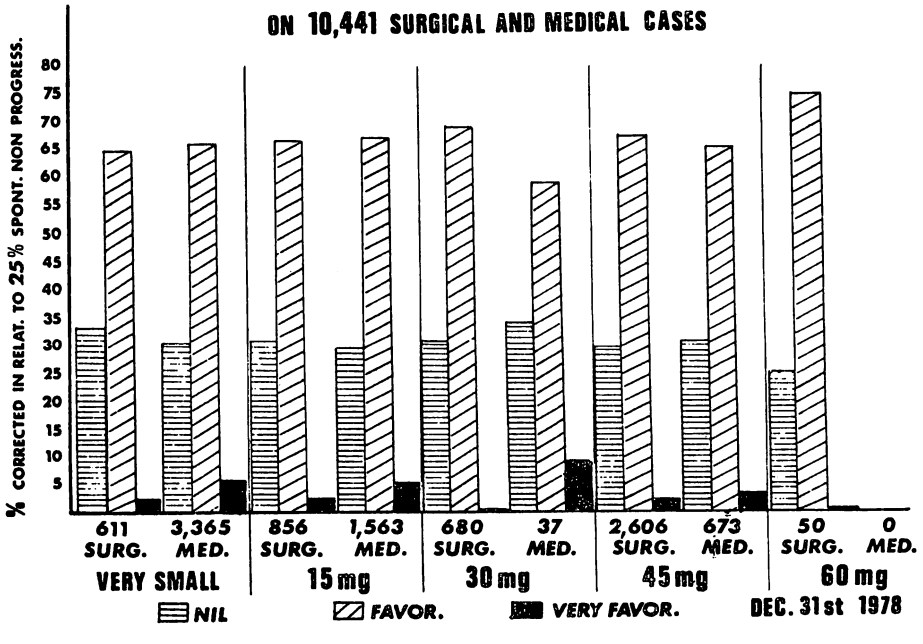
These results have been recently confirmed by an important paper, which stated that the administration of a combination of calcium gluconate, sodium fluoride, and vitamin D controlled vestibular symptoms in a high percentage of patients who had vestibular symptoms, and diminished tinnitus and arrested deterioration in hearing in patients who had cochlear symptoms.[46] The action of NaF on vestibular symptoms was also supported in 1972.[47]

CONCLUSION

Currently, the otospongiotic disease, generally called "otosclerosis," is no longer the disease confined to the niche with a stapedial fixation but is a disease of the whole otic capsule, with numerous and intricated foci constituted by innumerable otospongiotic microfoci.

The authors' enzymatic concept of the otospongiotic disease is based on numerous anatomic findings and extended enzymatic research; it was recently verified by some experimental investigations on animals, allowing histologic, biochemical, electrophysiologic, and impedancemetric studies to be performed.

This research led the authors to a better knowledge of the innermost mechanism of the disease itself, and thus to determine a postoperative medical therapy intended for supporting stapedectomy.



The medical management of otosclerosis surgery consists of an immediate postoperative therapy, for instance vasodilators, hypertonic glucose solution, and cortisone, and of a maintenance therapy, of which the best enzymogenesis regulator is the NaF originated by Shambaugh.

This medical management of the otospongiotic disease seems valuable, safe, and effective, as it appears from the functional results computerized in our otology clinic.

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