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SCIENTIFIC SECTION

Biomedical Research

Effects of oral supplementation with stable strontium

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The biologic effects of stable strontium, a naturally occurring trace element in the diet and the body, have been little investigated. This paper discusses the effects of oral supplementation with stable strontium in laboratory studies and clinical investigations. The extent of intestinal absorption of various doses of orally administered strontium was estimated by determining serum and tissue levels with atomic absorption spectrophotometry. The central observation is that increased oral intake produces a direct increase in serum levels and intracellular uptake of strontium. The results of these studies, as well as those of other investigators, demonstrate that a moderate dosage of stable strontium does not adversely affect the level of calcium either in the serum or in soft tissues. In studies of patients receiving 1 to 1.5 g/d of strontium gluconate, a sustained increase in the serum level of strontium produced a 100-fold increase in the strontium:calcium ratio. In rats, studies indicate that an increase in intracellular strontium content following supplementation may exert a protective effect on mitochondrial structure, probably by means of a stabilizing effect of strontium on membranes. The strontium:calcium ratio in animals receiving a standard diet is higher in the cell than in the extracellular fluid; this may be of physiologic significance.

An increase in density that corresponded to the deposition of stable strontium was observed in areas of bone lesions due to metastatic cancer in patients receiving stable strontium supplementation. This suggests the possibility of using strontium to mineralize osteophenic areas and to relieve bone pain. Also, because of reports of an inverse relation between the incidence of dental caries and a high strontium content in drinking water, the use of natural water containing relatively high levels of stable strontium should be considered. In each of these instances it is important to maintain a normal dietary intake of calcium.

Peu d'études ont été effectuées sur les effets biologiques du strontium stable, un oligo-élément naturel retrouvé dans la diète et dans l'organisme. Cette publication commente les effets de l'administration par voie orale de suppléments de strontium stable à la lumière d'études de laboratoire et d'essais cliniques. Le niveau d'absorption intestinale de différentes doses de strontium administrées par voie orale a été mesuré par détermination des taux sériques et tissulaires au moyen de la spectrophotométrie d'absorption atomique. La principale observation porte sur la hausse marquée des taux sériques de strontium et de son captation intracellulaire directement produite par l'augmentation de la prise de strontium par voie orale. Les résultats de ces études, tout comme ceux d'autres investigateurs, démontrent qu'une dose moyenne de strontium stable n'a pas d'effet délétère sur les taux de calcium dans le sérum ou les tissus mous. Chez les patients qui ont reçu de 1 à 1.5 g de gluconate de strontium par jour on a observé une augmentation soutenue du taux sérique de strontium, ce qui a provoqué une multiplication par un facteur de 100 du rapport strontium:calcium. Des études chez le rat portent à croire qu'une augmentation de la teneur en strontium intracellulaire suivant la supplémentation pourrait exercer un effet protecteur sur les structures mitochondriales, probablement dû à un effet stabilisateur du strontium sur les membranes. Chez l'animal qui reçoit un régime alimentaire régulier le rapport strontium:calcium est plus élevé dans la cellule que dans le liquide extracellulaire; ceci a possiblement une importance physiologique.

Une augmentation de la densité correspondant au dépôt du strontium stable a été observée dans les régions de lésions osseuses dues au cancer métastatique chez les patients prenant des suppléments de strontium stable. Ceci est une indication de la possibilité d'utiliser le strontium dans la minéralisation des régions ostéoporotiques et pour le soulagement des douleurs osseuses. Également, des rapports ayant fait état d'une proportion inverse entre l'incidence des caries dentaires et une forte teneur en strontium dans l'eau potable, l'utilisation d'une eau naturelle ayant une teneur relativement élevée en strontium devrait être envisagée. Dans tous ces cas on souligne l'importance de maintenir un apport calcique suffisant.

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The illustration on the cover of this issue of the Journal is a fragment of a map prepared by Robert Cooper in 1733. The map was based on a survey done by Alexander Bruce of the Loch Sunart area in Argyllshire, Scotland. It shows the village of Strontian and the nearby mining community of New York, where rock containing strontium was first discovered in 1787. The map was obtained through the courtesy of Brian Jackson, head of library services in the department of geology of the Royal Scottish Museum in Edinburgh, Scotland.

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Stable strontium has an unusual medical history. Ore containing this element was discovered around 1787 near the Scottish village of Strontian by Adair Crawford and his assistant, William Cruikshank, "surgeons and chemists to the Royal Artillery".[1] The strontium element was isolated, along with several other alkaline earths, by Sir Humphrey Davy in 1808.[2] For many years it was used mainly to produce fireworks because of the crimson-red colour it imparts to flames. It was not until 1883 that the physiologic effects of salts of stable strontium were recognized by Sydney Ringer during his experiments on frog's heart.[3]

The medicinal use of strontium salts was first described in *Squire's Companion to the British Pharmacopoeia* in 1884.[4] Subsequently strontium was introduced into the pharmacopeias of Great Britain, the United States, France, Germany, Spain, Italy and Mexico.[1] The element was used in combination with other compounds, such as in strontium salicylate, and in the treatment of various diseases (for example, strontium cinnamate was administered to cancer patients) on a purely empiric basis and without detailed knowledge of its action. Blumenbach, one of the early students of the use of strontium, did note that "strontianite is not poisonous to animals".[1] However, although toxic or side effects from strontium compounds were never reported, the clinical use of strontium gradually decreased, probably owing to a lack of understanding of its properties. As late as 1955, strontium compounds were still listed, but as medications available by prescription only.[5]

More recently there has been confusion in the public mind between the terrifying effects of radioactive strontium, a product of atomic fission,[6,7] and the effects of stable strontium, a naturally occurring trace element. Thus, stable strontium fell into disrepute because of an undue association with radioactive strontium, and the clinical use of stable strontium has nearly ceased. Possibly because of this confusion, the early work of Shorr and Carter[8] and of McCaslin and Janes[9] on the beneficial effects of stable strontium in the treatment of postmenopausal osteoporosis did not receive sufficient attention.

The purpose of this paper is to report on investigations of the mode of action of stable strontium and to review possible clinical applications of this element. Among trace elements present in sea water, strontium has the highest concentration, and it is widely distributed in the geosphere; it has been identified in all organisms that have been analysed.[10] Although stable strontium is a chemical analogue of, and interacts with, calcium, its absorption in the intestines and its biologic activity do not seem to adversely affect those of calcium — a point of physiologic significance that should be emphasized. The effects of strontium should be investigated within the framework of increased dosage of trace elements rather than that of replacing calcium. Recent evidence points out that oral supplementation of trace elements, beyond the levels required to correct a deficiency, may be needed or desirable in certain pathologic conditions.

Experiments on the effects of stable strontium in animals

Strontium:calcium ratio following an increased oral intake of strontium

In marine animals following changes in the strontium concentration of sea water: Of the calcium and strontium in vertebrates, 99% is located in bone. To investigate the effects of stable strontium on soft tissues it was found necessary to "bypass" the bone-seeking properties of this element. Initially the concentration of strontium in artificial sea water was changed and the effects of these changes on cellular processes were determined in soft tissue samples of "boneless" animals — marine coelenterates. It was not possible to produce an absolute strontium deficiency owing to the presence of strontium in calcium salts. However, in studies on polyps of *Podocoryne carnea* an increase in the concentration of strontium in sea water resulted in an increase in the amount of strontium absorbed by these animals but effected no change in their calcium levels.[11] In studies on the sexual form of *P. carnea* — the medusa (jellyfish) — an increase in growth rate and a higher resistance to intense aeration of water was observed in animals kept in sea water containing a high concentration of strontium. These studies were not completed because of the death of my colleague, Dr K.C. Hong.

In rats following oral intake of stable strontium Male adult rats of the RVH hooded strain were allowed to feed freely on a standard laboratory diet and were divided into groups according to the concentration of strontium chloride in their drinking water. In the experimental groups $SrCl_2$ was added to tap water in concentrations of 0.09%, 0.19% and 0.34%. A control group received tap water that contained 3.51 mg/dl of calcium, 0.68 mg/dl of magnesium and 0.02 mg/dl of strontium. A normal oral intake of calcium was maintained in all groups. The animals were weighed and examined weekly. Over a 3-month period the experimental animals almost uniformly showed a moderate increase in body weight and no adverse effects of the increased strontium intake. In longer-term studies no toxic effects were observed either in rats that received strontium supplementation in these dosages over a 3-year period or in those bred for three generations that were given such supplementation.

All determinations of the levels of calcium, magnesium and strontium in the animals' serum were carried out by standard atomic absorption spectrophotometry. Concentrations of these elements in brain, lung, heart, skeletal muscle, liver, spleen, adrenal and kidney tissue were determined by heated graphite atomization.

Changes in the ratio of strontium to calcium in the serum of animals receiving stable strontium supplementation are shown in Table I: the mean ratio increased linearly with increases in the concentration of the strontium supplement, while the levels of calcium and magnesium remained within normal limits.

Except for bone, animal tissues did not indicate any specific predilection for strontium. In the group receiving the most concentrated supplement the highest

strontium level was found in kidney tissue, followed, in order, by lung, adrenal, brain, heart, muscle and liver tissue. The strontium:calcium ratio in liver, heart, muscle and bone tissue is recorded in Table II, which shows that while a small proportion of calcium was replaced by strontium in bone tissue, calcium levels in soft tissue were not decreased by strontium supplementation. In the animals receiving a normal diet the strontium:calcium ratio was higher in the soft tissues than in the serum, possibly owing to cellular uptake.

These results indicate that the level of strontium in the serum rises following an increase in the oral intake of the element, whereas the levels of calcium and magnesium remain virtually unchanged. As a result, the normal ratio of strontium to calcium (1:1550) increases markedly. It was demonstrated originally by Schachter and Rosen,[12] and confirmed by numerous other investigators, that calcium, in addition to being diffused, is absorbed by an active process that is affected by serum levels of vitamin D and, as shown by Wasserman and colleagues,[13] by calcium-binding protein. Strontium, in comparison, is absorbed from the intestinal lumen by passive diffusion only, as evidenced by the increases in content of strontium in the serum that were in proportion to the amount taken orally. This lack of an absorptive limit for strontium does not invalidate the findings of Comar and Wasserman,[14] who have shown conclusively that when equal doses of radioactive calcium and radioactive strontium are administered, calcium is absorbed preferentially and strontium is excreted preferentially. In our experiments the intake of calcium and that of strontium were not equal: the calcium intake remained unchanged, whereas the strontium intake was increased progressively, although still remaining much below that of calcium. If a minor decrease in the serum level of calcium occurred, it was readily compensated for by a transfer of calcium from bone to blood and soft tissues, without adverse effects on bone metabolism. An important study in chicks contributed significantly to dispelling earlier misconceptions that stable strontium has a toxic effect on bone by showing that increases in the dietary intake of strontium do cause it to displace bone calcium, but without any deleterious effect until very high doses are taken.[15] The doses used in our experiments were much lower than those administered in this study in chicks, and we saw no evidence of any adverse changes in bone tissue. Stable strontium, when administered orally in increased dosages, should be considered as a separate entity and not as a replacement for calcium. No other trace element replaces a bulk element in its function.

Intracellular content of stable strontium

Changes in the intracellular content of calcium play a significant role in mediating chemical processes that affect the control of enzyme activities. Intracellular calcium levels are regulated by calcium pumps that operate in the plasma membrane and in the subcellular organelles (mitochondria, endoplasmic reticulum and sarcoplasmic reticulum). A considerable amount of data has accumulated in the biochemical literature indicating that calcium transport by mitochondria exerts a significant influence on the cytosolic concentration of calcium.[16-18] Studies by Rasmussen and associates[19,20] have demonstrated the importance of the mitochondrial uptake of calcium for intracellular messenger systems. Carafoli and Crompton[21] have recently drawn attention to the fact that although long-term maintenance of a low intracellular concentration of calcium depends on

Table I—Mean levels of strontium, calcium and magnesium, and mean ratio of strontium to calcium in serum of groups of six rats, by concentration of stable strontium added to their drinking water

Added strontium chloride (%)	Level, mean ± SD* (mg/dl)			
	Sr^{2+}	Ca^{2+}	Mg^{2+}	$Sr^{2+}:Ca^{2+}$
None	0.0064 ±0.0024	9.92 ±0.61	2.24 ±0.14	1:1550
0.09	0.192 ±0.023	9.63 ±0.42	2.36 ±0.85	1:50
0.19	0.380 ±0.025	10.21 ±0.25	2.41 ±0.23	1:27
0.34	0.868 ±0.211	10.11 ±0.17	2.28 ±0.19	1:12

*Standard deviation.

Table II— Mean levels of strontium and mean strontium:calcium ratio in tissues of groups of six rats receiving either no stable strontium supplementation or 0.34 mg/dl in their drinking water

Tissue analysed	Control group			Group given supplement		
	Level, mean ± SD (mg/dl)			Level, mean ± SD (mg/dl)		
	Sr^{2+}	Ca^{2+}	$Sr^{2+}:Ca^{2+}$	Sr^{2+}	Ca^{2+}	$Sr^{2+}:Ca^{2+}$
Liver	0.014 ±0.002	10.60 ±0.26	1:757	0.598 ±0.12	11.78 ±0.57	1:20
Heart	0.026 ±0.004	12.56 ±1.15	1:483	1.071 ±0.13	10.78 ±0.92	1:10
Striated muscle (gastrocnemius)	0.023 ±0.001	16.2 ±0.6	1:704	0.977 ±0.18	17.78 ±1.1	1:18
Adrenal	0.073 ±0.02	19.36 ±0.27	1:265	1.154 ±0.49	25.6 ±2.6	1:22
Brain	0.05 ±0.01	33.9 ±9.7	1:678	1.09 ±0.13	18.8 ±5.0	1:17
Bone	0.659 ±1.13	24 743.3 ±3 729.3	1:3753	1 111.6 ±192.8	23 931.9 ±1 056.4	1:21

the ejection of calcium through the plasma membrane, the short-term regulation in response to metabolic requirements or sudden fluctuations in its concentrations must depend on transport systems in intracellular organelles. The surface area of mitochondria is much greater than that of the plasma membrane: in the liver the mitochondrial surface area is 54.8% of the total surface area available for transporting calcium, as compared with 11.4% for the plasma membrane; in the heart the corresponding figures are 87% and 0.08%.[21]

The amount of data available on the intracellular strontium fluxes, which were used to obtain data on intracellular calcium metabolism, is much smaller. A recent article by Tashmukhamedov and Gagelgans[22] gives a detailed review of the interaction of strontium ions with mitochondria. The original studies of Carafoli and colleagues[23-26] established a basis for considering differences between the mitochondrial uptake of strontium and of calcium in vitro. Three aspects of their results are of particular interest:

- Mitochondrial swelling induced by a high concentration of calcium in the medium was not observed with high concentrations of strontium.
- Strontium appeared to exert some protective effect against spontaneous mitochondrial swelling as well as that induced by thyroxine, oleate, phosphates and calcium.
- The protective effect of strontium on mitochondrial function increased in proportion to the strontium concentration and to the strontium:calcium ratio in the medium.

Since the concentrations of strontium in these in vitro studies were very high, it was reassuring from a clinical viewpoint that no mitochondrial swelling was observed following administration of the strontium.

In our studies of intracellular strontium, stable strontium was added to the drinking water of male adult rats in the same concentrations and under the same experimental conditions as were described for our studies of strontium:calcium ratios in the serum. Subcellular fractions of liver tissue were separated by ultracentrifugation according to the method of De Duve and coworkers.[27] The quality of these preparations was checked by electron microscopy and by enzymatic methods. The mean concentrations of strontium, calcium and magnesium in the subcellular fractions of the control animals and of those given the medium concentration of strontium supplementation are shown in Table III. In the control animals the intracellular strontium:calcium ratio appears to have been one order of magnitude (approximately 10-fold) higher than the serum ratio (Table I). In rats receiving stable strontium supplementation the strontium content in the mitochondria (Fig. 1) increased, but the calcium content did not change significantly, with the result that the mitochondrial strontium:calcium ratio

FIG. 1—Liver mitochondria in rats receiving strontium supplement (0.19 mg of $SrCl_2$ per decilitre of tap water). Granules containing strontium (S) are more dense than those containing only calcium (C). The density of the calcium granules is very similar to that of the ribosomes (R) and membranes (Me). RER = rough endoplasmic reticulum.[28]

Table III—Mean levels of strontium, calcium and magnesium in the subcellular fractions of the liver in groups of 10 rats receiving either no stable strontium supplementation or 0.19 mg/dl in their drinking water

Cellular fraction	Control group: Level, mean ± SD (µg/100 mg of protein)				Group given supplement: Level, mean ± SD (µg/100 mg of protein)			
	Sr^{2+}	Ca^{2+}	Mg^{2+}	$Sr^{2+}:Ca^{2+}$	Sr^{2+}	Ca^{2+}	Mg^{2+}	$Sr^{2+}:Ca^{2+}$
Mitochondria	0.121 ±0.027	25.43 ±6.63	77.05 ±14.00	1:210	0.538 ±0.068	22.39 ±4.86	69.04 ±7.73	1:42
Lysosomes	0.089 ±0.012	20.47 ±5.28	88.33 ±8.55	1:230	0.466 ±0.07	18.83 ±4.83	88.95 ±9.77	1:40
Microsomes	0.087 ±0.02	17.77 ±2.93	96.52 ±10.76	1:204	0.449 ±0.08	15.59 ±2.03	92.64 ±7.68	1:35
Cytosol	0.023 ±0.005	3.55 ±1.60	61.93 ±6.62	1:177	0.106 ±0.044	3.34 ±1.93	61.24 ±4.66	1:31

rose. Similar increases in the strontium:calcium ratio occurred in the lysosomes and microsomes and in the cytosol, indicating a general increase in cellular strontium content and equilibration with the strontium:calcium ratio in the serum. Although the strontium content of the cellular membrane was not measured, it is probable that some strontium was retained at the membrane. We previously reported data from experiments (carried out in a different laboratory at McGill University) that indicated that the strontium:calcium ratio was higher in the cytosol than in the cellular organelles.[29] These data were not substantiated in the present study. However, both studies showed that the membranes of liver cells and those of cellular organelles permit an increase in strontium diffusion and a subsequent rise in intracellular strontium levels without any deleterious effect on or significant changes in cellular levels of calcium and magnesium. Strontium, unlike other divalent cations, shares reactive sites involved in membrane transport systems with calcium, including sites of low and high selectivity.[30] According to data presented by Porzig,[30] the energy stored in the cell membrane in the inwardly directed electrochemical gradient for sodium can be used for the outwardly directed transport of calcium and probably strontium. Porzig's findings also indicate that the inward movement of strontium induces a calcium outflow.

Extensive studies have been carried out on different types of physiologic mitochondrial swelling in vitro. One research group observed that the topologic changes in the inner mitochondrial membrane essentially did not differ from other configurational changes.[31] There is no uniformity of opinion about the structure of this membrane. Sjöstrand and Cassell[32] recently suggested that a distinction should be made between the inner surface membrane and inner cristae membranes. Their suggestion may be significant with regard to the morphologic characteristics of the membrane changes in pathologic mitochondrial swelling in vivo, since such a suggestion implies that cristae membranes may be distinct structures connected to the inner mitochondrial membrane.

Unlike physiologic mitochondrial swelling, pathologic swelling results in a disruption of the inner mitochondrial membrane and a permanent change in mitochondrial structure that are synonymous with mitochondrial injury. Tashmukhamedov and Gagelgans[32] pointed out that the damaging effect of calcium and the stabilizing effect of strontium on mitochondrial structure may be a result of the differences between the effects of these cations on mitochondrial phospholipase A_2, an enzyme located in the external mitochondrial compartment. Strontium seems to inhibit this enzyme when a saturation point in the intramitochondrial calcium content is reached, whereas calcium activates it.[32] The results of our preliminary electron microscopic studies in rats indicate that when mitochondrial damage was produced in the liver by bromobenzene (0.2 ml/100 g body weight injected intraperitoneally) the mitochondrial structure was better preserved in animals receiving stable strontium in tap water (0.19 mg/dl) than in control animals.[33] In rats subjected to exhaustive exercise (60 minutes' running on a motor-driven treadmill), the mitochondrial swelling — recorded as the degree of loss of cristae structure — was significantly greater in the control group than in the animals receiving stable strontium supplementation.[29] Further studies are necessary to determine the extent and types of mitochondrial injury that may be ameliorated by a high intracellular content of strontium.

Table IV—Mean serum levels of strontium and calcium and strontium:calcium ratio in serum of 100 subjects taking a normal diet* and 50 patients receiving stable strontium supplementation†

Population	Level, mean ± SD (mg/dl) Sr^{2+}	Ca^{2+}	$Sr^{2+}:Ca^{2+}$
Control subjects	0.0053 ± 0.0039	9.432 ± 0.55	1:2247
Patients	0.5128 ± 0.198	9.449 ± 0.96	1:18

*The normal dietary intake of Sr^{2+} is approximately 2 mg/d.
†They received 1 to 1.5 g/d of strontium gluconate, which provided 183 to 274 mg/d of Sr^{2+}.

Clinical observations

Supplementing a diet that provided the usual amount of calcium with stable strontium for patients with osteoporosis was first proposed by Shorr and Carter,[8] who reported a marked reduction in bone pain. McCaslin and Janes[9] undertook a long-term study of patients with postmenopausal osteoporosis, using physical and roentgenographic criteria to evaluate the results. (Atomic absorption spectrophotometry was not available at that time to correlate the blood levels of strontium with the physical findings.) A significant clinical improvement was observed in 84% of the patients who had taken strontium lactate orally for periods ranging from 3 months to 3 years. These investigations demonstrated that there is a wide margin of safety in the amount of stable strontium intake in human subjects, since doses of up to 1750 mg/d of strontium ion did not produce any side effects.

Our clinical studies began by determining strontium and calcium levels in 100 subjects who were receiving a regular diet that supplied approximately 1 g of calcium and 1 to 2 mg of strontium a day. Table IV shows strontium and calcium levels in the serum of these patients. Since stable strontium is not a new drug, with the approval of appropriate authorities I administered 0.1 to 1.5 g/d of strontium gluconate (183 to 274 mg Sr^{2+}) for periods of at least 3 months to 50 of these patients with various conditions that might be affected by stable strontium: metastatic bone carcinoma, cachexia, postmenopausal osteoporosis and hepatic cholestasis. The mean level of strontium in the serum of these patients increased, while the calcium level did not change significantly (Table IV). A single oral dose of 0.5 g of strontium gluconate administered to a fasting subject resulted in a marked increase in the serum strontium concentration, with the peak being reached in 4 hours; the level decreased rapidly in the next 72 hours (Fig. 2), and then gradually over a 4-week period. The level of calcium in the serum of

this patient was 9.7 mg/dl before the strontium was given and 9.4 mg/dl 72 hours later. This response to a single dose of strontium confirms the early observation of Harrison and colleagues[34] that 15% of the strontium was retained at day 30 following an oral dose of strontium chloride.

Studies by Warren and Spencer[35] provided other data on strontium metabolism. Daily oral doses of 1537 mg of strontium (administered as strontium lactate) for periods ranging from 24 to 36 days resulted in a positive strontium balance in all subjects. Following a daily intravenous infusion of stable strontium (612 mg of Sr^{2+} administered as strontium gluconate) for 6 days, patients kept on a low-calcium diet excreted each day an average of 235 mg of strontium in the urine and 60.2 mg in the feces. The first study demonstrated that humans can retain considerable amounts of strontium ion without any toxic effects, and the study showing high rates of strontium excretion also indicated that strontium is not firmly bound to the crystalline lattice of bone but, after its administration is stopped, is replaced by calcium. These studies also showed that the percentage loss of the retained strontium is similar whether 300, 600 or 900 mg of strontium was infused intravenously. El Solh and Rousselet[36] observed that in rats that were kept on a diet supplying a normal amount of calcium there was a decrease in the level of calcium in the serum and marked calcinuria following the intravenous injection of stable strontium. (These findings may indicate that an intravenous injection of strontium could be used to treat disorders involving abnormally high levels of calcium in the serum.)

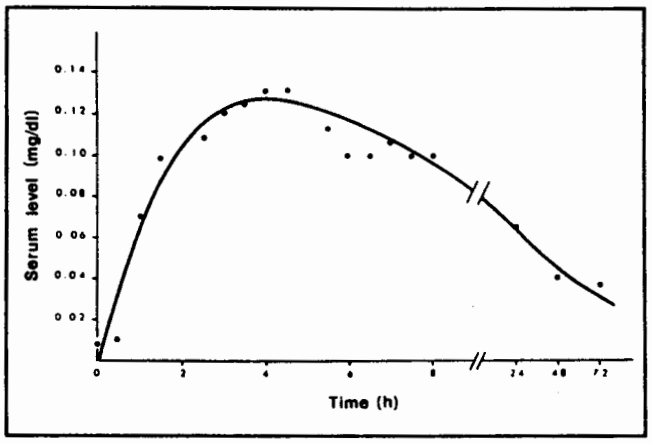

FIG. 2—Serum levels of strontium following oral administration of 0.5 g of strontium gluconate to a fasting subject (S.C.S.).

In the group of 50 patients that received stable strontium for 3 months or longer the number of cases of the various conditions was too small to make statistically valid comparisons, but the mean strontium: calcium ratio in the serum of these patients did increase to 1:18, compared with 1:2247 in subjects not given the supplement. No side effects or toxic reactions were observed, and 73% of the patients gained an average of 2 kg of body weight over 2 to 3 months. Subjective feelings of improvement, which are impossible to evaluate, particularly in cancer patients, were frequently reported. In patients with metastatic bone cancer arising from a primary lesion in the breast or prostate, roentgenographic studies showed mineralization of metastatic lesions (Figs. 3 and 4). Deposition of strontium in these lesions can be recognized roentgenographically because of the high density of strontium resulting from its high atomic weight. Also of interest is the occurrence of a sclerotic halo around some of the osteolytic metastatic lesions in the pelvis (Fig. 5).

FIG. 3—Mixed osteoclastic and osteoblastic lesions of body of second lumbar vertebra due to metastatic carcinoma of left breast in (A) April 1980, before stable strontium supplementation began, (B) June 1980, after 3 months of supplementation, and (C) December 1980, 6 months after cessation of supplementation. Progressive strontification, increased sclerosis and improvement of definition of anterior margin of body of vertebra are evident.

Further studies involving a larger number of patients are necessary to determine whether strontification of metastatic lesions affects metastatic growth.

However, it does appear that a moderate increase in strontium intake has no adverse effects on calcium metabolism. Toxic or side effects were not reported in subjects who took strontium for years in doses of 200 to 400 mg Sr^{2+}/d.[1,5] To what extent oral supplementation of strontium beyond that given to correct a deficiency is desirable is a question not unlike that regarding supplementation of other trace elements, such as chromium[37] and zinc.[38] In patients with conditions such as metastatic bone cancer for which no treatment is available, strontium could be useful for palliative care. An optimal daily dose of strontium for patients with postmenopausal osteoporosis or alcoholic hepatitis remains to be established.

Discussion

The central fact that can be deduced from our observations is that a marked increase in serum levels and in cellular uptake of strontium corresponds with increases in the amount of strontium taken orally. The results of the present investigation as well as those of others studying animals and humans[8,9,15,36,39] indicate that a moderate daily dose of stable strontium does not adversely affect either calcium levels in the serum and soft tissues or bone metabolism as long as a normal dietary intake of calcium is maintained. In human subjects receiving approximately 200 to 300 mg/d of Sr^{2+}, the strontium:calcium ratio averaged 1:18, compared with 1:2247 in those receiving a standard diet. The marked increase in the strontium:calcium ratio is undoubtedly due to an increase in the strontium level in the serum, although the absolute amount of stron-

FIG. 5—Osteolytic pelvic lesions arising from carcinoma of left breast in patient receiving stable strontium supplementation. A thin sclerotic margin (arrows) can be seen surrounding the lesions.

FIG. 4—Multiple osteoblastic lesions of pelvis due to metastatic carcinoma of prostate in (A) October 1979, before stable strontium supplementation began, (B) April 1980, after 3 months of supplementation, and (C) January 1981, while supplementation was continuing. Last panel shows marked progression of sclerosis, particularly involving ischium.

tium is still small compared with that of calcium. Strontium salts were administered in this dosage range to patients for decades during the first half of the 20th century, either as a carrier for other compounds or in the treatment of various conditions, without evidence of any toxic or other side effects.[4,5] Since accurate methods of measuring strontium content were not available at that time, the strontium:calcium ratios in these patients were never calculated. It is apparent that whereas the calcium content of body fluids and tissue is under the strict homeostatic control of hormonal mechanisms, the strontium content can be increased significantly, a fact that may have therapeutic implications.

Also of interest was the relatively high strontium: calcium ratio in the cytosol and cellular organelles of animals receiving a normal diet; the ratio was at least one order of magnitude higher than that in the serum. In the course of the evolutionary process, mechanisms have developed that maintain a low intracellular level of calcium in order to regulate numerous enzymatic and nonenzymatic reactions; yet these same mechanisms allow a relatively high level of intracellular strontium and thus a high strontium:calcium ratio. Furthermore, they permit a significant increase in the intracellular strontium concentration without adverse effects. The physiologic significance of these findings is not known. They certainly pose an interesting problem in developmental biology.

Considering the possible clinical significance of a high mitochondrial level of strontium, we do not at present have sufficient data to decide whether the stabilizing effect of strontium on mitochondrial structure is due to changes in the permeability of the inner mitochondrial membrane or to an effect on structural protein–phospholipid complexes. Tashmukhamedov and Gagelgans[22] postulated that oscillatory changes in mitochondrial levels of calcium due to influx–efflux activity produce changes in the inner mitochondrial membrane: calcium activates phospholipase A_2, releasing the products of hydrolysis of phospholipids with resulting damage to mitochondrial structure. This phenomenon may be related to the displacement of magnesium by calcium from binding sites: an efflux of bound magnesium, the element currently regarded as the physiologic stabilizer of mitochondrial structure,[40] would result in destabilization of the inner mitochondrial membrane. Further data on intercompartmental fluxes of calcium and strontium are necessary to determine the mechanisms involved at the cellular level.[41] What appears to be established is that mitochondrial phospholipase A_2, which is activated by calcium, is inhibited by strontium.[22]

Although cellular responses to injury are undoubtedly affected by a number of factors, it is conceivable that mitochondrial injury plays a significant role in these responses once the damage to mitochondrial structure reaches a point of no return — a stage at which mitochondrial function becomes affected. Among other pathologic conditions, ultrastructural mitochondrial changes were observed in alcoholic hepatitis,[42] and in ischemic injury of the heart[43] and striated muscle.[44] Anghileri[45] suggested that mitochondrial injury resulting from an excessive calcium influx, following changes in membrane permeability that are produced by carcinogens, is a significant phenomenon observed in a variety of tumours. This observation, which relates magnesium:calcium ratios to the regulation of the replication of deoxyribonucleic acid, deserves further investigation as a possible factor contributing to the induction of malignant transformation; perhaps the effect of mitochondrial damage as a factor contributing to the progression of cancer is not dissimilar to that of intercellular junctional deficiencies demonstrated in cancer tissue by Loewenstein.[46] If carcinogenesis is conceived of as a sum of alterations in different cellular processes not necessarily affected by the same factors,[47,48] it is possible that alterations in mitochondrial structure affect some cellular characteristics, such as invasiveness, but not others, such as growth. In a previous article it was suggested that in several types of cancer in human subjects, such as those of the stomach, breast and prostate, the lack of a carcinogenic common denominator is apparent and that the development of cell autonomy may be the result of nonspecific contributory processes rather than the action of a single carcinogen.[49] Although currently available data do not permit a definition of a stochastic model of carcinogenesis,[50,51] structural mitochondrial damage deserves further study, as was indirectly indicated by Warburg.[52] However, we have no evidence to regard it as a final cause of cancer with respect to meeting the criteria of probability.[53]

Effects of stable strontium on bone

The effects of stable strontium on bone should be discussed separately since it replaces bone calcium when the oral intake of strontium is increased. The replacement of calcium by massive doses of strontium (1.5% to 3% of the dietary intake) is disadvantageous since this has been shown to produce bone changes in experimental animals that were originally described as "strontium rickets".[39] Similar changes were observed when animals were fed diets low in calcium and high in strontium.[54-57] The bone lesions produced in these studies cannot be ascribed to the high level of strontium but rather to the decrease of bone calcium.

Studies in vitro on the physicochemical properties of bone mineral crystals[58] and of the collagenous matrix derived from tendon[59] provide some indications as to why calcium and not strontium was "selected" during the evolutionary process as a more suitable structural element for the skeleton. The development of the ability to select calcium as a necessary element for the growing skeleton appears to be related to improvements in the mechanisms of absorption and excretion of calcium. According to Gunatilaka[60] the bone content of strontium in animals decreases "as they make evolutionary advances from [an] aquatic to [a] terrestrial habitat", although notable exceptions exist that may be due to differences in environmental levels of strontium.

These observations, which concern the relative roles of calcium and strontium in physiologic bone forma-

tion, do not apply to pathologic conditions. In metabolic diseases of bone tissue, recalcification of osteopenic areas does not usually occur, possibly owing to a strict homeostatic control of the calcium level in the plasma that does not permit a transfer of calcium to decalcified regions. This may be the reason why calcium supplementation therapy has not completely fulfilled expectations. Not only does a transfer of strontium to bone occur, but also the deposition seems to take place preferentially in areas of active bone remodelling.[61] This would explain our observation that relatively small oral doses of strontium led to remineralization of bone lesions due to metastatic cancer. Strontium deposits that may have prevented vertebral collapse were detected in one patient several months after the cessation of strontium supplementation (Fig. 3).

Further studies, particularly morphometric investigations, are necessary to determine the nature of the changes occurring in bone following strontium supplementation. Calcium uptake by the mitochondria of bone cells,[62] as well as in other organs, such as the liver[63] and the kidneys,[64] has been amply demonstrated. Strontium in the mitochondria of soft tissue organs forms amorphous aggregates that appear as granules.[65] Inoue[28] has demonstrated strontium-containing granules in liver mitochondria of rats receiving stable strontium supplementation. Mitochondrial strontium in bone cells appears to have a definite crystalline structure.[66] The extent to which bone cell mitochondria participate in the processes of matrix vesicle formation and mineralization cannot be determined on the basis of available data.

There can be little doubt that the cause of osteoporosis is multifactorial[67-71] and that in any therapeutic approach the formation of bone matrix as well as mineralization should be considered. The rationale for using strontium to treat postmenopausal osteoporosis is complex. Storey,[39] in a discussion of the clinical studies of McCaslin and Janes,[9] suggested that strontium has beneficial effects because it inhibits the resorption of bone by covering endosteal bone surfaces with an osteoid that is resistant to resorption. Estrogens were shown to prevent bone loss in postmenopausal osteoporosis: not only did they seem to directly inhibit bone resorption,[72] but also, as shown by Cruess and associates,[73] they may affect phospholipid complexes. Because strontium also seems to inhibit bone resorption and affect phospholipids by as yet undetermined mechanisms, perhaps strontium may be used concomitantly with estrogens, since it is desirable to decrease the dosage of estrogens to levels at which the incidence of endometrial cancer is not increased. Another possibility is to combine stable strontium with fluorides: if fluoride increases bone formation, preparations such as strontium fluoride may be useful by simultaneously promoting bone formation and inhibiting bone resorption.

Mechanisms underlying the beneficial effects of drinking water with a high strontium content on dental caries may be similar to those operational in metabolic bone diseases. The association between a low incidence of dental caries and an increased strontium intake was shown by studies on caries resistance in US Navy recruits[74] and by the epidemiologic surveys of Curzon and associates.[75] The results obtained in studies in rats were less convincing, perhaps because, as with fluoride, a much higher level of strontium in drinking water is needed to produce a cariostatic effect in rats.[76] However, Gedalia and associates[77] demonstrated a significant reduction in the incidence of caries when administering $SrCl_2$ (25 mg/l of drinking water) to hamsters prior to tooth eruption. There are also reports that when $SrCl_2$ is used to fill root canals it inhibits periapical inflammatory changes.[78] Further studies are required to ascertain the optimal levels of strontium in drinking water. Such levels may be higher than those present in municipal drinking water. The Montreal area provides a good example of a community in which there is a significant difference between the strontium content of municipal drinking water and that of the area's well water, which usually reflects the strontium content of the soil: the municipal water content of Sr^{2+} is 0.19 mg/l, whereas its well water content varies between 2.3 and 3.2 mg/l.

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