1976

# STRONTIUM - BIOCHEMICAL INTERACTIONS AND INHIBITIONS IN ANIMALS AND MAN

by

CHERYL ANN CATOR SMYERS

A.A.S., Morrisville Agricultural and Technical College
State University of New York, 1972

B.S., Rochester Institute of Technology, 1974

---

A MASTER'S REPORT

submitted in partial fulfillment of the

requirements for the degree

MASTER OF SCIENCE

Department of Foods and Nutrition

Kansas State University
Manhattan, Kansas

1977

Approved by:

Kathleen Newell

Major Professor

Document
LD
2668
.R4
1977
S61
C.2



# TABLE OF CONTENTS

# ILLEGIBLE DOCUMENT

THE FOLLOWING DOCUMENT(S) IS OF POOR LEGIBILITY IN THE ORIGINAL

THIS IS THE BEST COPY AVAILABLE

**THIS BOOK CONTAINS NUMEROUS PAGES WITH DIAGRAMS THAT ARE CROOKED COMPARED TO THE REST OF THE INFORMATION ON THE PAGE.**

**THIS IS AS RECEIVED FROM CUSTOMER.**

# INTRODUCTION

Knowledge of minor elements in animal and human nutrition is of continuing interest. By definition, trace elements, minor elements, or micronutrient elements are "chemical elements that are distributed throughout the tissues in very small amounts and are either essential in nutrition...or may be harmful..." (1).

At one time, strontium, a trace element found in human tissue, was believed to be beneficial, but further studies have identified its damaging properties. Originally discovered from a lead ore and barytes mine in the Northwest Highlands of Scotland by Sir Alexander Murray in 1722, stable strontium and its radioactive isotopes now appear to threaten man's health. Radioactive forms of strontium are by-products of uranium fission within a chain reaction pile. Fallout carries radioactive strontium throughout the atmosphere making man's food chain susceptible to contamination.

When strontium contaminated plant and animal sources are ingested, both stable and radioactive forms are deposited in the skeletal system of the body. With the deposition and retention of radioactive strontium in body tissues, irreversible internal radiation damage occurs by the relentless beta-particle emission during it's radioactive half-life. Absorption of radioactive strontium predisposes human beings to two forms of carcinoma, leukemia and osteosarcoma.

Age, dietary calcium and phosphorus intake levels, and physiological status are factors that affect strontium

accumulation in the body. Researchers believe that diets containing concentrated stable strontium inhibit calcium absorption and synthesis of intestinal calcium-binding protein. Inhibition results from blockage at the 25-hydroxycholecalciferol conversion site in the kidneys.

Methods have been developed to measure the levels of radioactive strontium retention and their inhibitions. Therapeutic trials with radioactive strontium tracers have shown several metabolic sites of physiological discrimination in the body. Stable strontium metabolism, under conditions of normal dietary intake, is controlled by natural discriminatory mechanisms in man and animals throughout their life cycles.

Current strontium research developments suggest a counteractant which completes the calcium absorption cycle by avoiding strontium inhibition. Although tested in laboratory animals only, extracts from calcinogenic botanical sources and structural analogs have been demonstrated to be effective in stimulating calcium absorption by overcoming inhibition and enhancing the body's natural discriminatory ability. However, this has not been substantiated with human studies.

# REVIEW OF LITERATURE

## Inorganic Chemistry

Strontium, characterized by an atomic number of 38 and an atomic mass of 87.62 daltons, belongs to the alkaline earth family. It is grouped with five elements known to be hard metals: beryllium, magnesium, calcium, barium, and radium. Their oxides have properties that are between alkali and earth elements. Strontium normally occurs in the +2 oxidation state and is strongly electropositive. This bivalence is created by the presence of two electrons in the outer s shell of each neutral atom. Since the electrons are released with comparative ease, a stable electronic structure, such as found in an inert gas, results with two residual positive charges in the nucleus (2). However, an univalent state of strontium ions has been detected in conductivity and freezing point studies of the molten strontium halide in equilibria (2).

Strontium (originally called strontia) was first distinguished from barium carbonate in 1790 by A. Crawford of Edinburgh from a lead mine in Strontian, Scotland (3). Davy, in 1808, electrolyzed metallic strontium with mercuric oxide and isolated the free metal (4).

Because of strontium's reactivity, it is always found in nature as a compound rather than in the free state. In its natural state, strontium is composed of four stable

isotopes: $^{84}Sr$, $^{86}Sr$, $^{87}Sr$, and $^{88}Sr$ (5). Their average relative abundance on a unit basis is as follows: 0.56%, 9.86%, 7.02%, and 82.56%, respectively. Strontium is twenty-second in atomic abundance of elements present in igneous rock. Twelve remaining unstable radioactive isotopes also exist. They are: $^{81}Sr$, $^{82}Sr$, $^{83}Sr$, $^{85}Sr$, $^{89}Sr$, $^{90}Sr$, $^{91}Sr$, $^{92}Sr$, $^{93}Sr$, $^{94}Sr$, $^{95}Sr$ and $^{97}Sr$ (6).

Upon bombarding, a mixture of the four naturally occurring stable isotopes of strontium with neutrons, produces the radioactive isotopes. The number of isotopes produced is dependent on the nuclear properties of the original four isotopes, the proportions present, and their individual neutron energies. More specifically, the nuclear property of an isotope will determine its ability to receive a neutron, or its neutron capture cross-section (2). After isotopes are formed, they tend to decay by loss of electrons ($B^-$) or positrons ($B^+$) or by orbital electron capture, depending upon the neutron capture cross-section ability of the individual isotope. The cross-section of the nucleus is the collision probability between the nuclear size and the bombarding particle (2). The isotope's neutron capture cross-section character also will affect materially the length of the half-life period. Characteristically, most radioactive isotopes have long half-lives and limited activities. A half-life is the time in which the radioactivity originally associated with a sample of isotopes will be reduced by one half through radioactive decay. The

half-life of the remaining sample will be equal in duration to that of the original specimen (1). Adequate availability and lengthy half-life periods are required for successful radioactive tracers (2).

Strontium oxides, hydroxides, carbonates, and sulfates are the most common chemical combinations found in nature. SrO, a white solid oxide with a melting point of 1300-1400$^{0}$, tends to react slowly with moisture and carbon dioxide in air to form the hydroxide or carbonate. The exothermic reactions are (2):

$$SrO + H_2O \longrightarrow Sr(OH)_2$$

$$SrO + CO_2 \longrightarrow SrCO_3$$

Strontium peroxide, $SrO_2$, strontium superoxide, strontium octahydrates and dihydrogen diperoxides are also known, and are formed by hydrating suitable grades of strontium oxide.

Formed strontium hydroxides are used in refining of beet sugar. Strontium hydroxide, $Sr(OH)_2$, forms by rapid exothermic reaction of cold water with the carbonate(2):

$$SrCO_3 + H_2O \longrightarrow Sr(OH)_2 + CO_2$$

When strontium hydroxide reacts with acid, hydrogen and the divalent cation evolve vigorously (5).

Carbonates of all alkaline earth metals are distributed widely. Strontium carbonate, $SrCO_3$, is a primary source of other strontium salts and chemicals, and is highly stable to heat. Strontium ions have the largest lattice structure found in aragonite rock (2).

Strontium combines energetically with other non-metal elements to form ionic compounds of halides, hydrides, nitrates, sulfides, and other complexes. The halides of strontium include strontium chloride, strontium bromide, and strontium iodide. Generally, strontium dihalides exist as very soluble white crystalline solids, and are formed by dissolving strontium carbonate in the specific halogen acid. Bromide and iodide strontium forms are found commonly in medications as pharmaceuticals and sedatives.

Strontium hydrides, $SrH_2$, are insoluble in common organic and inorganic solvents. They are strong reducing agents that liberate hydrogen, and can be used as drying agents, and a portable hydrogen source. Crystalline hydrides of strontium resemble mica.

Nitrites, nitrates, nitride halides, and azides are prepared by direct combination of the elements with strontium. Strontium nitrate, produced by reacting nitric acid with the carbonate or oxide forms a monoclinic crystal as a tetrahydrate when placed in a cold solution (2). When the anhydrous salt combines with combustible elements, such as carbon and sulfur, the volatile salts impart a crimson color to flames. This procedure is used in the production of pyrotechnical products.

Sulphides, selenides, tellurines, and phosphors, have properties dependent on the purity of the strontium material. Strontium sulfate occurs as an anhydrous mineral; it is insoluble and has no known physiological effect. Sulfites

and bisulfites of strontium are formed easily and decompose to sulfur dioxide when heated. The phosphides, phosphines, phosphites, hypophosphites, phosphates, insoluble hypophosphates and strontium acid salts can be prepared also.

**Boronides,** carbides, and acetylides can be produced and are marginally stable. Strontium forms anhydrous aluminates, silicates and aluminosilicates, that are isomorphous with magnetoplumbite, and salts of oxyacids with hypochlorites, anhydrous perchlorates, hydrates and ammoniates. Titanates of strontium occur naturally as impure compounds. However, titanates prepared from double strontium oxalate provide an extremely high refractive index of the boule, and are more common (2). Their optical disperisons are almost as high as that of diamonds, and the gemstones are very brilliant.

Organometallic compounds of strontium include alkyl and aryl derivatives. Cyclopentadienyls of strontium are rather unstable, and occurrence of dialkyls has been reported. Complexes of strontium form only with ligands having strong donor properties, such as ammonia. Other strontium compounds include acetates, alkoxides, chlorates, and permanaganates.

## Occurrence

Strontium is distributed commonly throughout the earth's crust. As an alkaline earth element, strontium is found in igneous rock with insoluble minerals and complexed with silicates. The estimated percent composition of strontium

in the earth's crust is $1x10^{-2}$ (7). Strontium deposits tend to leach through the soil by weathering; it is never found in the free state, but rather, because of its low electronegativity, it bonds with nonmetallic elements such as oxygen.

Its distribution is controlled by the extent that strontium can substitute for $Ca^{2+}$ ion in common calcium-bearing rocks. This reaction is governed by the ability potassium feldspar can act as a cation exchange resin and substitute $Sr^{+2}$ for $K^{+}$ ions (8). The bivalent vapors are in an eight-fold coordination that enables strontium to act as a dispersed trace element in igneous rocks, and become concentrated to form its own minerals as in hydrothermal deposits and carbonate rocks. Its chief mineral deposits are celestite, $SrSO_4$, and strontianite, $SrCO_3$. These compounds are very similar to the corresponding calcium compounds in both physical and chemical properties. Celestite is more abundant than strontianite, and it is very slightly soluble only in acids. It is light blue to white in color, transparent in thin layers, and translucent in mass. Strontium metal is prepared by electrolysis of the fused chloride mixed with potassium chloride, or by reduction of strontium oxide with aluminum in a vacuum furnace at temperatures which distill off strontium (4).

Strontium is deposited in igneous rocks such as plagioclase feldspar and apatite, where strontium ions have replaced calcium ions (8). Strontium is found also in pyroxenes and biotites.

Traces of strontium occur in nearly all limestone and dolomites, and small amounts are present in natural brines of high calcium chloride and low sulfate content (2). Mitchell (9) states that limestones contain about 1,000 ppm strontium, and dolomites contain less, sometimes much less than 100 ppm. Strontium is involved initially in the crystalization of magma, and decreases in concentration as the magma cools. Average concentrations of strontium in rock types are listed in **table** 1 (8).

Strontium deposits are located at or near some tide waters. In studies at the East Bay of Port au Port Bay, Canada, strontium was found frequently with deposits of barium and barium sulfates (10). There are many areas of strontium mining. Celestite ore is mined in Gloucestershire and Somersetshire, Great Britian. Other areas of celestite deposits include Sicily, Italy, Mexico, United States, Canada, USSR, France, India, and Tunisia. Mexico is the chief source of high grade celestite in North America. Germany is the largest producer of strontianite ore from limestone deposits in Westphalia, Prussia.

General uses of strontium compounds include munitions, tracer bullets, tracer shells, signal flares, star shells, and other pyrotechnical signals and fireworks. Furthermore, strontium compounds are used in the production of fillers and brightners for paints, lacquers, plastics, hard rubber, linoleum, asphaltic materials, and as fluxing agents for

TABLE 1

Average concentrations of strontium in terrestrial rocks and chondrite meteorites in ppm (8).

| Sample | ppm |
|---|---|
| Chondrites | 10 |
| Crust | 375 |
| Ultrabasic rocks | 2.32-72.4 |
| Basalt | 465 |
| Syenite | 300 |
| Granodiorite | 450 |
| Granite | 285 |
| Shale | 300 |
| Greywacke | 400 |
| Quartzite | 450 |
| Limestone | 500 |

steel melting, where high concentrations of sulfur and phosphorus exist. Other uses are in chemical, pharmaceutical, and ceramic processes. Metallic strontium has no commercial use, but small quantities are applied in the alloying process of copper with tin and lead. Strontium has been replaced by less costly substitutes since its current cost is \$14.95[1] per pound.

Although naturally occurring strontium contains four stable isotopes, fourteen radioactive isotopes can be prepared from it artificially. These short-lived radioactive isotopes are used to date various rocks and minerals. Radioisotopes are of great value in tracing biological compounds in vivo and in vitro (11). In tracer studies, $^{89}Sr$ and $^{90}Sr$ isotopes are used, normally. These beta-emitters are often used to determine radioassessment in fission product and fallout studies with a Geiger or other proportional counter. In neutron-activated Sr samples, $^{85m}Sr$, $^{85}Sr$, $^{87m}Sr$, and $^{89}Sr$ are observed; $^{89m}Sr$ is present rarely. These isotopes are used most commonly for short-lived monitoring of gamma rays measured by scintillation counter or spectrometer. Whem fission product mixtures are used, mass numbers above $^{88}Sr$ are present. Radioactive $^{91}Sr$ and $^{92}Sr$, emitting both beta and gamma radiation of short half-lives, can be counted with Geiger, proportional or scintillation counters. Because of the excessively short half-lives, other beta emitters, $^{93}Sr$,

---

[1]Turtox/Cambosco. (1977-78) Catalog. MacMillan Science Co., Inc., Chicago, Illinois.

$^{94}Sr$, $^{95}Sr$, and $^{97}Sr$, can not be observed accurately. In tracer studies using those short-lived isotopes, they are permitted to decay undetected as long as isotopes of $^{89}Sr$ and $^{90}Sr$ are measured.

Radioactive $^{90}Sr$ is of greatest importance because of its longer half-life than other isotopes. With a half-life of 28 years, it is one of the best long-lived high energy beta-emitters known, and of special interest in the development and use of SNAP (Systems for Nuclear Auxillary Power) devices (4). SNAP devices are used in space vechicles, remote weather stations, navigational buoys and other transmission equipment requiring a lightweight, long-lived, nuclear-electric power source. However, despite the importance of $^{90}Sr$ for transmission purposes, it presents a health hazard as a nuclear fall-out product.

## Method of analysis

There are many methods of analysis that can be used for the determination of strontium in biological and inorganic systems. These include general qualitative and semiquantitative methods as suggested by Goodenough and Stenger (2).

In classical analyses, strontium cations are removed by precipitation with chlorides, sulfides, or hydroxides. Strontium is always present as a member of a triad with calcium and barium. All three are precipitated by adding ammonium carbonate in the presence of ammonium hydroxide and

ammonium chloride. The hydroxyl-ion concentration is lowered by the chloride to prevent magnesium hydroxide from precipitating. The resulting carbonate forms are tested for strontium individually by dissolution in a minimum of dilute hydrochloric or nitric acid. The presence of strontium or barium is ascertained by the formation of a white precipitate from the element in a saturated solution of calcium sulfate. During separation, barium is precipitated with dilute solutions of potassium dichromate in aqueous acetic acid. When excessive strontium is present, it is precipitated with calcium by ammonium oxalate in dilute acetic acid.

In order to identify the presence of strontium, a flame test is conducted followed by analysis of the emitted color by a prism spectroscope. Strontium is observed as brick red, calcium as orange-red, and barium as green (7). Currently, approximate quantitative analysis for strontium is based on this procedure of spectral lines or bright-line emission spectrum (7). Flame photometry, emission methods of arc or spark spectrography, and atomic absorbance measurement yield comparable results.

Christian has reviewed the procedures for determination of strontium by flame photometry, atomic absorbance, and emission spectroscopy (12). Gravimetric and titrimetric methods of quantitative analysis of strontium are used rarely because of the natural complexes with calcium, and the relative scarcity of strontium.

Neutron activation analysis is the most sensitive detection method for strontium and x-ray fluorescence is the second. Neutron activation analysis is very sensitive for analyzing trace elements, because only a few radioactive atoms are necessary for detection. Sensitivity of analysis is dependent on the neutron flux, the cross-section from the neutron capture by the element, the half-life of the induced radioisotope, and the time of irradiation (13). A principle advantage of neutron activation analysis is that the sample needs no ashing, and, once it is activated to total radioactive conversion, little danger of contamination occurs because of the minute sample required. The x-ray fluorescent method requires the irradiation of a strontium sample. Radiant energy from short wavelengths such as gamma rays, x-rays, ultraviolet rays or of kinetic energy from fast-moving particles such as beta and alpha particles, are used to excite strontium atoms to emit radiant energy of a wavelength that can be detected and recorded (7). These emissions can be observed and recorded on photographic material.

Isotope dilution mass spectrometry (positive ray analysis) is used for strontium determination in geochemical studies. It shows the relative isotopic abundance of a sample as detected and described by the intensities of the lines obtained on either the mass spectrograph, mass spectrometer, radian spectrometers, magnetic lens spectrometer, crossed-field spectrometers, or sector spectrometers (14). Jury and his

co-workers (15) used flame photometry, neutron activation, spectrochemical and emission spectroscopy to determine strontium content in living tissues.

Radiochemistry of strontium

Radiochemical analysis is essential for the control of and protection from radioactive materials and atomic energy. Many methods are used to monitor environmental contamination and radioactive waste disposal. Contamination of foods is the most important concern. Radioactivity occurs naturally, but the greatest concentration is generated from nuclear energy.

Most naturally occurring radioactive isotopes have a high nuclear charge and mass. Nuclei that exist with a charge greater than 83 are considered radioactive. Isotopes with charges of 81, 82, and 83 are unstable (14). There are a few existing radioactive isotopes with lower charges.

In many cases, radioactive strontium isotopes are produced by neutron reactions resulting from fission. When uranium is bombarded, four $B^-$ activities are produced, and through neutron capture, complete rupture of the uranium nucleus occurs. Lanthanum (La), strontium (Sr), yttrium (Y), and inert gas, xenon (Xe) or krypton (Kr), or an alkali metal cesium (Cs) or rubidium (Rb) are produced (14). Isotope products of early radioactivity experiments were $^{85}Sr$, $^{89}Sr$, and $^{90}Sr$, that deteriorated by beta-particle emission and had

lengthy half-lives. Radioactive $^{85}Sr$, emitting gamma radiation, has a half-life of 64 days; $^{89}Sr$ has a half-life of 53 days with a breakdown to $^{89}Y$ which is stable; and $^{90}Sr$ has a half-life of 28 years with a breakdown to $^{90}Y$, that further deteriorates to $^{90}Zn$, the stable form. These successive transformations of chain branching from radioactive strontium to yttrium during their natural disintegration series are related to their individual chemical properties in accordance with the following displacement laws (14):

1. When an element emits an alpha particle, the product has the properties of an element two places to the left of the parent on the periodic table.

2. When an element emits a beta particle, the product has the properties of an element one place to the right of the parent on the periodic table.

In the radioassay of solutions containing radioisotopes of strontium, particular attention is paid to the individual decay schemes and emitted radiation. Of considerable importance are the half-life, type of radiation, and energy of radiation. In general, radiochemical analysis is conducted by adding a known amount of stable strontium isotope as a carrier for the radioactive strontium isotope sought, and after purification of the sample, the measured radioactivity is corrected for chemical yield by the amount of carrier

recovered. In cases where no stable isotopes exist, the nearest stable element from the same periodic group is used as a carrier. An alternate method of chemical yield determination is the use of a known amount of another radioactive isotope as tracer for the radioactive isotope sought (16).

The radioassessment of $^{90}Sr$ is of greatest importance because it has the longest half life; it is a common fallout pollutant and has limitless exposure to the food chain of man. Alkali fusion and acid leaching are methods that are used, commonly for the identification of $^{90}Sr$ in soils. Following appropriate chemical treatment and depending on the soil's composition and construction, Geiger or scintillation counters may be used for radioassessment of $^{90}Sr$. A major problem in $^{90}Sr$ analysis exists when the stable strontium content surpasses that of the original specimen.

Many sources of radioactive strontium contamination exist. The major concern of $^{90}Sr$ environmental contamination pertains to its consequences in human beings. The tentative basis for the analysis of $^{90}Sr$ contamination is based on the maximum permissible concentration levels for the radionuclide in air and water as recommended by the International Commission on Radiological Protection. The levels for $^{90}Sr$-$^{90}Y$ are $2x10^{-10}\mu c/cm^3$ in air and $8x10^{-7}\mu c/cm^3$ in water (17). The more hazardous radionuclides include alpha emitters and $^{90}Sr$-$^{90}Y$, a beta-gamma-emitting radionuclide.

Other radioassays of dissolution are used to determine the strontium concentration in animal and human bone ash, milk, vegetable ash and water. In all determinations, the ashed sample is dissolved in nitric acid in the presence of the strontium carrier. The nitric acid concentration is then increased to precipitate all the strontium and separate any barium and calcium carriers present. Storage of strontium is allowed for particular time periods so the yttrium may grow and be milked off and counted. Then strontium is precipitated as a carbonate and in most cases mounted and counted. Through this analysis, individual strontium nuclides are obtained and maximum information is gathered.

Rate of radioactive contamination

Environmental contamination is the deposition of a radioactive material in any place where it is not desired and particularly where its presence may be harmful or constitute a radiation hazard (1). One quarter of the radiation received is from space, as natural background radiation, and the remainder results from radioactive isotopes in rocks, soils, waters and atmosphere. Man has actually contributed to these amounts by his experiments with nuclear fission. The worldwide dissemination of radioactive strontium, its transport, and its distribution are monitored by man.

Of the more than 90 different occurring radioisotopes identified among fission products, $^{90}Sr$ has been of public

concern for a considerable time. It is not a normal biological reactant, and by its calcium resemblance, its radioactivity gives rise to leukemia and bone tumors. Radioactive testing in the late 1950's produced at least 140 pounds of $^{90}Sr$ (18).

The distribution of $^{90}Sr$ is dependent upon the type and location of the explosions. Surface explosion over land tends to vaporize and irradiate large amounts of soil. At least 80 percent of the fallout lands in an irregular elliptical pattern downward from the original explosion site within a few hours. In the case of water, close-in fallout drops as low as twenty percent of the total (18).

Upon detonation, fission products swirl no higher than the troposphere. Convection currents in the lower layer of the atmosphere readily mix air from higher altitudes, so as to prolong the fallout distribution months at a time. Likely enough, the winds of the troposphere rarely cross the equator, and therefore most fallout remains in the hemisphere of origin. Stratospheric fallout receives the thrust from high-yielding nuclear test. Once these areas are saturated, fallout remains aloft for long periods of time. Stratospheric fallout accounts for two-thirds of the total and is the dominant artificial radioactive fallout source (18). As $^{90}Sr$ compounds slowly drifts across the soil, it becomes engulfed in the chemical

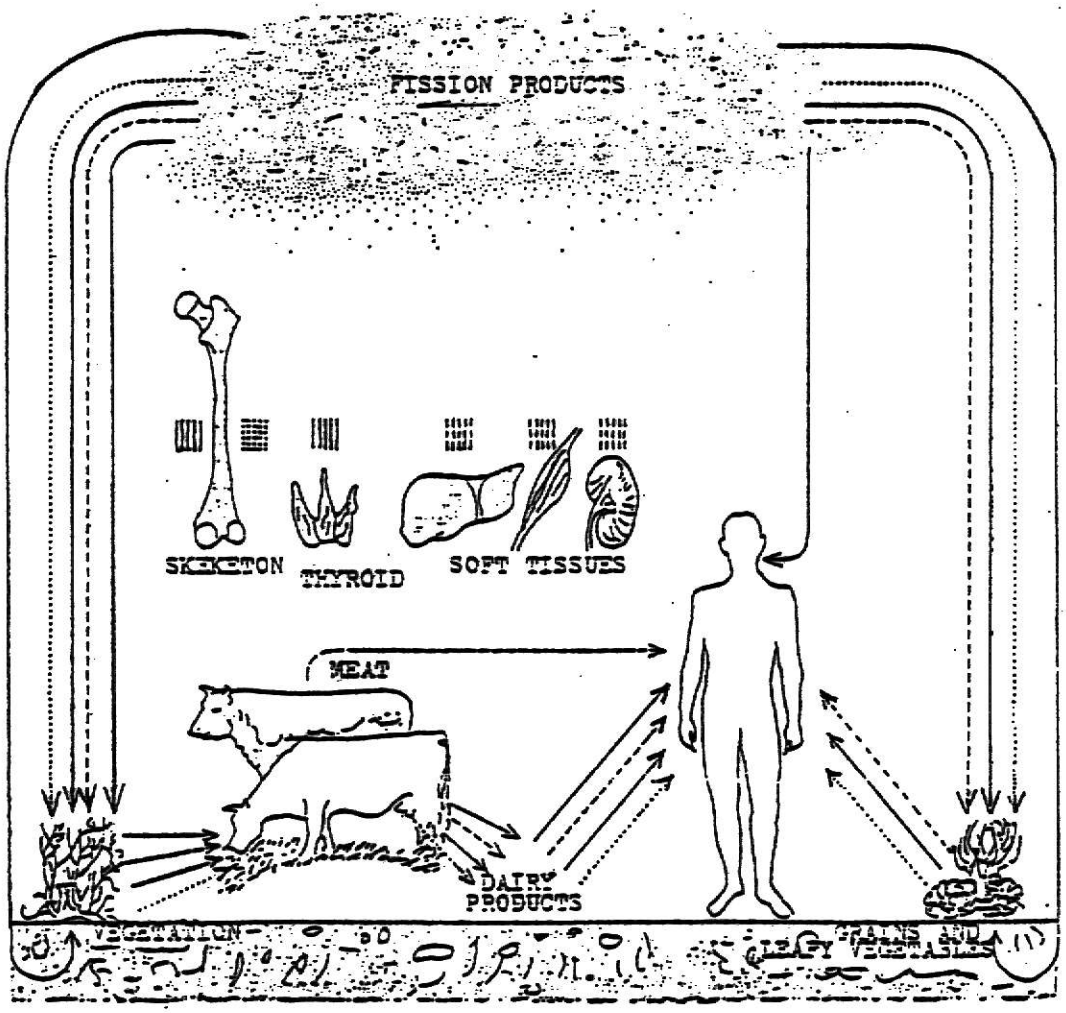


Fig. 1. Paths of entry by which fallout, $^{90}Sr$ and $^{89}Sr$, reach man through the soil (18).

biosphere of living cells and tissues. Then the rate of contamination becomes dependent on the rate at which $^{90}Sr$ deposits from the air on the soil. The paths by which $^{89}Sr$ and $^{90}Sr$ enter the food chains of man are indicated in figure 1 (18).

Air and water

The two principal modes of entry of radioactive materials are through air inhalation and water and food ingestion. Radiation exposure from air inhalation is inescapable by animals and man. Only insoluble nuclides and alpha emitters are considered airborne radioactive materials. Air is the primary vehicle of strontium dispersion from the site of the explosion to the site of deposition (19). The existing levels of radioactivity found in the air should not exceed the maximum permissible concentrations recommended by the International Commission on Radiological Protection. As $^{90}Sr$ fallout is deposited on vegetation, it may be consumed directly or indirectly by both animal and man.

Water, if directly contaminated, can be a predominant source of $^{90}Sr$ nuclides, but is only a small contributor to the overall environmental contamination. Surface waters are contaminated with radioactive particles by rainfall, surface run-off, and liquid wastes from uranium mining and milling operations. Additionally sources of contamination may be

nuclear fuel production from the conversion of uranium concentrates, nuclear reactor installations using air or water as coolants, nuclear fuel reprocessing plants, hospital radionuclide diagnosis and therapy units, radioisotope laboratories and industrial applicators (17). Generally, ground waters with naturally occurring radionuclides have lower concentrations of radioactivity than do surface waters. Chemical treatments of surface waters do not remove strontium radionuclides.

Strontium nuclides are leached from the soil surface into the ground water supply. The rate at which $^{90}Sr$ moves through the soil strata into the water supply is dependent upon its solubility and the degree to which it is adsorbed and/or exchanged with the constitutents of the soil, and the extent of water table movement (19). Once $^{90}Sr$ reaches the ground water table, the rate of soluble movement increases with the anion concentration, cation magnitude, and the presence of acids, alkalis, salts, and other complexing agents. This progression is usually slow enough that most of the radioactivity introduced originally has decayed before the ground water is used for drinking purposes.

However, ground water can be an indirect source of radionuclide contamination by its use for crop irrigation. Contamination can occur also from foliar and flood irrigation. Those two types of irrigation are common for $^{90}Sr$ deposition on plants. Radioactive materials may reach the tissues of

plants by contaminated water introduced into the soil and absorbed by plant roots along with nutrients.

## Soil and plants

Radionuclides are contained in the soil or are subject to airborne recontamination as they lie on the surface of the soil. Radioactive materials are deposited in the soil through lateral and downward movement. Lateral movement occurs when heavy rain and surface wash cause the radioactive material to be moved from bare land to other land surfaces or into water sources. The extent of movement is dependent on the intensity and distribution of rainfall, the topography, and the composition of the soils. These factors alone cause extensive movement of $^{90}Sr$. Downward movement of radioactive materials occurs from mechanical displacement of particles, such as by deep plowing, or by their independent movement as free ions. On cultivated land, they are mixed uniformly throughout the soil. Soil fauna, such as earthworms, and natural drying and cracking of soil, followed by subsequent rainfall contribute to the downward movement of particles. Mechanical mixing by heavy rains in highly arid areas will cause a similar displacement effect. However, without mechanical mixing, penetration by radioactive materials, such as $^{90}Sr$, is slowed. Numerous measurements of the distribution of $^{90}Sr$ in soils from world-wide fallout

have shown that the major fraction is retained for long periods of time in the upper layers of the soil (2). Furthermore, $^{90}Sr$ remains very non-uniformly distributed throughout the root zone in undisturbed soils for many years after deposition.

The extent to which radioactive ions move downward through soils is determined by the degree to which they are retained by exchange or absorption on mineral particles, and the extent of water movement by dispersion (19). Different types of soils and their ability for surface retention affect the penetration rate.

Water is the main agent of ion transportation and subsequent retention on mineral surfaces in the soil. Movement of $^{90}Sr$ in compounds is dependent on the compound's diffusion and mass flow properties (19). Soil can become a reservoir of long-lived $^{90}Sr$.

Generally, the soil mineral solutions bath the moisture absorbing roots of plants. As ions pass into the plant, the soil strontium concentration is lowered. From the aspect of plant physiology, a quantity of a nuclide can be absorbed by different sections of the plant from a solution, the principal source of direct contamination is from airborne radioactive materials. Soil absorption is a secondary source of direct contamination in the above-ground parts of plants; more direct absorption occurs through splashing rain or resuspension by wind. Retention of $^{90}Sr$ from fallout has

been estimated to be between 23 and 49% in above-ground plant parts (19).

The rate of contamination in soil and plants is dependent on the rate of deposition from the air. Variations in animal dietary contamination are dependent on fallout inconsistencies, the lag effects of annual fallout and cumulative deposit, and individual dietary habits. Absorption of strontium radionuclides in solution by leaves varies from plant to plant, and once absorbed, it is retained. There are three direct routes of absorption: through leaves as foliar absorption, through inflorescences or floral absorption, and through the basal portion and roots or plant-base absorption (19). The route of absorption is determined by the physical and chemical characteristics of the deposit, the environmental conditions at the time of deposition, and the biological characteristics of the plant, including its growth habit, physiological status and morphological characteristics. General leaf absorption of $^{90}Sr$ occurs to some degree through the stomata, but primarily through the epidermal cells. Significant foliar and floral absorption occur only if deposition is during the growth of an individual leaf or inflorescence. Materials are absorbed from the root mat of grass pastures for prolonged periods, because diluted soluble ions become fixed with soil minerals and are more freely available. Plant-base absorption of $^{90}Sr$, is more

significant than foliar absorption in herbage grazing of cattle. Mitchell (9) found grazings of red clover to have a mean of 74 ppm strontium, while the mean value for rye grass was only 15-18 ppm strontium.

Several additional factors tend to affect the plant uptake of radionuclides. They include differences in the chemical soil nature type, soil pH (low pH reduces the uptake of strontium), and the type of root system (shallow versus deep rooted). Variations in distribution of radioactive material affect greatly the quantity absorbed by plants with shallow root systems. Pasture grasses may absorb three times more radioactive strontium when it is present on the soil surface than when incorporated to a depth of 30 cm by ploughing (20).

Superficial contamination is lost readily from leaves by mechanical processes, leaching by rain, and airborne redistribution. In most cases, washings with water tend to remove fission products that were deposited several weeks previously. Further, because of its immobilization, little $^{90}Sr$ that enters the plant by foliar or floral absorption will reach the shoot or underground organs (21). Therefore, changing deposition rates and areas of absorption affect the overall contamination of the specimen. Also, animal feed processing that results in delay between production and animal consumption will alter the total contamination present.

Strontium tends to be associated with high calcium foods,

such as milk and green vegetables. The rate of contamination in cereals and vegetables is less than that found in milk, although direct contamination of leafy vegetables during heavy fallout periods will raise the normal levels. Bruce et al. (22) observed a two-month interval between $^{90}Sr$ soil deposition and its appearance in cow's milk.

## Animals

Studies (23) that considered the availability of $^{90}Sr$ to various Egyptian plants from environmental contamination showed that with fallout, direct deposition of fission products occurred on leaf surfaces, and the resulting contaminants were absorbed metabolically by the plant or transferred directly to animals (or man) that consumed the contaminated foliage. Foliar deposition is the most important mode of entry of $^{90}Sr$ into the food chain of animals.

Contaminated food-producing animals are of the greatest concern to man. There is naturally occurring variation in the metabolism of different species, but all species can become contaminated by strontium by absorption through the skin, air inhalation, and food ingestion (24). Domesticated animals of particular interest include dairy cows, beef cattle, sheep, swine, goats, fish and poultry. In most cases, absorption of $^{90}Sr$ by animals occurs through the consumption of radiocontaminated feed.

Ingested contaminants are absorbed into the body of the

animal from the gastrointestinal tract. Herbivorous animals have a large compartment in the alimentary canal where bulky, fibrous foods are delayed in passage to permit soaking and fermentation. Those ruminants having large stomachs are of special interest to dairy and meat producers, because the rate of passage of ingested foods governs the degree of absorption and subsequent irradiation. Generally, radionuclides of strontium are absorbed from the small intestine. The mechanisms of intestinal absorption include diffusion and active transport. Water-soluble vitamins, some nucleic acid derivatives and fat-soluble substances are absorbed by diffusion (24). Active transport provides a rapid and efficient transfer of substances, that are required by the organism, across the intestinal membrane. It is responsible for the absorption of most nutrients. The movement of a substance against an electrochemical gradient requires sufficient metabolic energy. Active transport is accountable for some strontium ion absorption. Furthermore, $^{90}Sr$ attaches to a membrane carrier, a protein-binding component of the cell wall, to move across the membrane to its inner surface. The amount of $^{90}Sr$ absorbed is governed by the relative rates of movement of Strontium and calcium ions across various membranes, gastrointestinal wall, the mammary cells and the placental barrier.

Following absorption, strontium enters the circulating

fluids of the body. Then nuclides are excreted in the urine and feces, deposited in various tissues and bone, transferred across the placental barrier for deposition in the fetus or secreted in milk (24).

Milk is the most important animal product that can carry environmental radioactivity to the human population. Milk secretion in the cow depends on the cow's genetic constituency, the condition of the animal, and the feeding management after parturition. Milk secretion is a continuous process. Radioactive substances enter the continually forming milk by rapid transfer from blood to milk. The rate of appearance of strontium nuclides in milk is governed by the rate at which they were absorbed and transferred to the blood stream (24). The total amount of radiostrontium secreted varies from .05-0.2% of the milk volume (24).

As stated earlier, animal products are the link in the food chain by which radionuclides reach man. The quantity of radioactive nuclides in animal products is dependent upon the amount ingested. Edible livestock tissue contains negligible amounts of strontium radioisotopes. Strontium-calcium ratios are used to express $^{90}Sr$ levels in animal tissue products. The major concern is the contamination level of milk and dairy products.

Aquatic animals concentrate certain radionuclides by direct intake of water and food or by direct passage through

epithelial membranes (17). Strontium tends to deposit in bones and shells of mollusks, rather than in soft tissues. The distribution of $^{90}Sr$ in the surface water of the Pacific Ocean has been calculated to be 1μμC/liter, and in other oceans one-tenth of that value (25). In fresh water environments, $^{90}Sr$ occurs in much higher concentrations than salt water.

In poultry relatively long-lived nuclides, that may be stored in feeds, are the only major source of contamination. Absorbed radionuclides can be transferred from the hen to the egg (17). The deposition of $^{90}Sr$ occurs mainly in the shell and yolk and less in the white. The shell protects the egg from external strontium penetration and any surface contact radiation can be washed away easily.

Man

As man ingests contaminated plant and animal tissues, stable strontium and $^{90}Sr$ are deposited in the body frame. Milk and vegetables have the highest concentration of stable strontium and $^{90}Sr$ radionuclides. In analyzing the effect of diet on stable strontium and radioactive strontium intake the intake of calcium must also be considered. The intake of calcium influences strontium metabolism (26), In man's diet, leaf and root vegetables contribute up to 15% of total strontium intake; eggs, meat, fish, and drinking

water contribute a small proportion, and milk and other dairy products contribute intermediate amounts. Differences occur however, depending on geographical location, regional customs and individual eating habits. Also differences in contaminated intake are accounted for by age, economic level, and social religious dictates.

**Strontium content of foods**

Analysis of strontium in foods has been conducted widely and periodically. As discussed earlier, neutron activation is the most sensitive method for strontium detection. X-ray fluorescence, flame photometry and emission spectroscopy are used less frequently. In order to determine additional strontium incorporation in tissue, the calcium content is expressed in ratio to the strontium content. The strontium-calcium ratio (Sr/Ca) is of much greater usefulness than monitoring strontium content alone. Values of $^{90}Sr$ are reported in relation to both calcium content and the weight of the product. The differential of strontium to calcium content is expressed as the Strontium-Calcium Observed Ratio (OR) and is defined as (25):

$$OR_{sample/precursor} = \frac{Sr/Ca \text{ of sample}}{Sr/Ca \text{ of precursor}}$$

The method of expression was developed to monitor the comparative movement of strontium and calcium in biological systems. This

concept permits (25):

1. Prediction of total body burdens from dietary intakes
2. Prediction of total diet values from tissue or excretion measurement and
3. Prediction of maximum $^{90}Sr/Ca$ ratios of any single mineral deposit in the body from diet measurement.

The values represent the ratio as actually available to the organism and as actually derived from a single precursor. The observed ratio (OR) of the body content to the diet shows that animals vary within a ratio of 0.18-0.35 Sr/Ca (25).

The radionuclides of strontium in a biological system behave similarily to the stable form and are governed by the calcium concentration with which they are interrelated in metabolism. Concentrations of radiostrontium are expressed in terms of the calcium concentration by the unit of pCi (picocuries or $10^{-12}$ curies) of radiostrontium/gram of calcium. In fluids strontium is expressed as picocuries of radiostrontium/liter (16).

The National Academy of Sciences has compiled data on strontium concentrations in foods from which a listing of foliar and soil fallout deposits in various foods is also available (27). Concentrations of $^{90}Sr$ found in various foods in 1968 are compiled in table 2, and in milled products in table 3 (27). Radioactive ion content, such as $^{90}Sr$, is dependent upon the refinement that the product undergoes before final measurement.

TABLE 2

Contribution of various foods to $^{90}Sr$ in New York City in 1968 (27).

| Food | pCi $^{90}Sr$/yr | Percent of total intake | |
|---|---|---|---|
| | | Ca | $^{90}Sr$ |
| Dairy products | 2080 | 58 | 38 |
| Vegetables | 1212 | 9 | 22 |
| Fruits, fresh and canned | 1192 | 3 | 22 |
| Cereals and bakery products | 588 | 20 | 11 |
| Meat, poultry, eggs | 178 | 8 | 3 |
| Fish | 5 | 2 | -- |
| Water | 200 | -- | 4 |

TABLE 3

$^{90}Sr$ values in wheat-milling products (27).

| Item | $^{90}Sr$ in 1959 crop | |
|---|---|---|
| | pCi/kg (range) | pCi/gCa |
| Wheat | 46 (20-63) | 113 |
| Patent flour | 9 (6-12) | 53 |
| First and second clear flour | 17 (9-37) | 63 |
| Germ and shorts | 143 (36-171) | 166 |
| Bran | 163 (70-237) | 142 |

Other dietary studies have been conducted by the United Nations' Food and Agriculture Organization, and the World Health Organization (28). A recent joint study by Feige and co-workers (29) in cooperation with the Food and Agriculture Organization, the World Health Organization, and the International Atomic Energy Agency showed a high concentration of the long-lived $^{90}Sr$ radionuclide in the Israelite diet.

Man absorbs more strontium through ingestion than inhalation. The increasing levels found in human diets show a pattern of absorption correlated with levels of contamination, the soil's ability for radionuclide uptake, precipitation, and the processing of the foodstuffs (29).

## Biological Interrelationships

For many years, strontium was considered to have some beneficial role in metabolism in both plant and man. Strontium was believed to play various metabolic roles including stimulation of plant growth, healing of fractures, and bone remineralization. Recently, research interest has been in the element's functioning as a fissionable material that interferes with the normal metabolic functions of calcium including bone mineralization, blood coagulation, contractility of muscles, and reactivity of the nervous system. Strontium in biological systems is assayed by its individual movement or by its comparative movement with calcium.

### Calcium affinity

Most strontium deposition, either stable or radioactive, is found in combination with calcium reservoirs. Not only is strontium found complexed with calcium, but also with barium. Strontium and calcium, with interlocking metabolic behavior, are linked biologically in terms of their deposition in foods, tissues, and bones. Calcium metabolism is controlled by homeostatic means, and regardless of variations in dietary intake of calcium, the levels found in blood and milk of the animal are held in constant balance with body needs. Strontium metabolism, is not under homeostatic control but is regulated instead by the level of calcium in the body (30). Their

metabolic schemes and chemical behavior are similar, however, calcium and strontium behave differently in physiological reactions. Primarily, calcium differs from strontium in its ability to regulate tissue development and fluid movement, such as in bone and plasma. Strontium imitates these functions by its dependence upon the serum calcium concentration for control of its function.

Comar (30) has suggested that the strontium to calcium ratio in the body is regulated by a two-compartment system in the kidney. The model consists of a small exchangeable pool and a large slowly filled one. The flow establishes a steady state ratio of strontium to calcium, especially in adults consuming a uniform diet. However, children who have not yet established a steady state condition because of sporadic growth and development, are more prone to strontium bone formation or urinary excretion as the calcium pool concentration fluctuates. Strontium uptake in stable or radioactive forms is always undesirable, because of its ability to replace calcium in bone formation. Within normal dietary ranges the stable strontium to calcium ratio, and the radioactive $^{90}Sr$ to Ca ratio in body tissues or secretions, will be related directly to the ratio that exists in the diet (5). Both calcium and strontium are absorbed to a limited extent from the gastrointestinal tract, depending on the vitamin $D_3$ status.

Vitamin D synthesis and calcium binding protein formation

Vitamin D and its metabolites are essential for intestinal calcium movement across cell membranes (31). Although there are two forms of vitamin D, ergocalciferal (vitamin $D_2$), and cholecalciferol (vitamin $D_3$), there is a greater formation and activation of the latter.

After vitamin D has entered the system there is a lengthy period prior to its activation. Activated vitamin D regulates (1) active transfer of intestinal calcium and phosphorus, (2) renal tubular reabsorption of phosphates and amino acids, and (3) skeletal mobilization of citrate concentrations in fluids and bones (31). This process is specific for calcium but not for cations of strontium. Vitamin $D_3$ is responsible also for the formation of the calcium-binding protein (CaBP) found in the intestinal mucosa. Analyzed transport systems suggest that the protein-binding factor in the intestinal mucosa necessary for binding the alkaline earths of calcium, strontium, and barium are induced by vitamin $D_3$ action (32). The small intestine is associated intimately with the transfer of calcium across the intestinal epithelium by an unknown molecular mechanism, and is the physiological site of vitamin $D_3$ action (33). Four high affinity sites exist for molecular calcium: the entire length of the small intestine, the surface coat of the microvilli the PAS-positive (para-aminosalicylic acid) cells, and the

goblet cells. Additional calcium binding sites are activated as the calcium concentration increases to $2 \times 10^{-3}$M in the blood (31).

In animal cells, cholecalciferol, a derivative of 7-dehydrocholesterol is of interest. The location of 7-dehydrocholesterol is in the epidermis, and as the skin is irradiated by sunlight, the circulating level of 25-hydroxycholecalciferol (25-OH-$D_3$) increases (33). Synthesis of vitamin D begins with its absorption in the presence of bile from the jejunum. It is transported to the liver by lymph chylomicrons where it is hydroxylated to 25-OH-$D_3$ (34). Hydroxylation, that occurs in the endoplasmic reticulum, is regulated by the level of 25-OH-$D_3$ present, and is supported by NADPH and molecular oxygen (33). Then it is transferred from the chylomicrons to the vitamin carrier globulin protein.

Activation is completed with hydroxylation of the liver metabolite to 1,25-dihydroxycholecalciferol (1,25-$(OH)_2D_3$) in the kidney mitochondria by utilization of Krebs cycle substrates and molecular oxygen (33). For characteristic physiological response, vitamin $D_3$must be converted to its metabolically active form. Calcium binding, bone resorption, and calcium transport will occur without this conversion, but not so efficiently as to prevent rickets (33). The most active metabolite is 1,25-$(OH)_2D_3$. However, when 1-hydroxylase is suppressed, two stereoisomers of 24,25-dihydroxycholecalciferol

(24R, 24,25-$(OH)_2D_3$ and 24S 24,25-$(OH)_2D_3$) are formed also in the mitochondria, but their functions are unknown (33). Some of the metabolites are indicated in figure 2. Following final hydroxylation, 1,25-$(OH)_2D_3$ is transported by blood to high calcium affinity sites. In the intestine it stimulates calcium binding protein synthesis for binding and active transport of calcium across the intestinal mucosal lining.

High concentrations of the metabolite stimulate increased calcium binding. The enzyme, 1-hydroxylase, is a mixed-function oxidase and is dependent on cytochrome P-450 and renal ferredoxin (33). Therefore, the extent of bone mineralization is correlated directly with the 1-hydroxylation mechanism of 1,25-$(OH)_2D_3$. Dietary and serum calcium concentration regulate 1,25-$(OH)_2D_3$ production. Increased serum calcium levels cause a decrease in 1-hydroxylase and stimulate 24,25-$(OH)_2D_3$ production (33).

The biological effectiveness of the conversion of 25-OH-$D_3$ to 1,25-$(OH)_2D_3$ can be monitored and assayed by measuring the plasma concentration. A dual assay utilizes the physiologic target tissue receptor, and may be the most valid assessment of the total activity of vitamin D level in a given plasma sample.[2] The target system is a high affinity

---

[2]Hughes, M.R., Brumbaugh, P.F. & Haussler, M.R. (1975) A dual assay for measuring the plasma concentration of 1,25-dihydroxyvitamin $D_3$ and 25-hydroxyvitamin $D_3$. Fed. Proc. 34, 893. (Abstract).

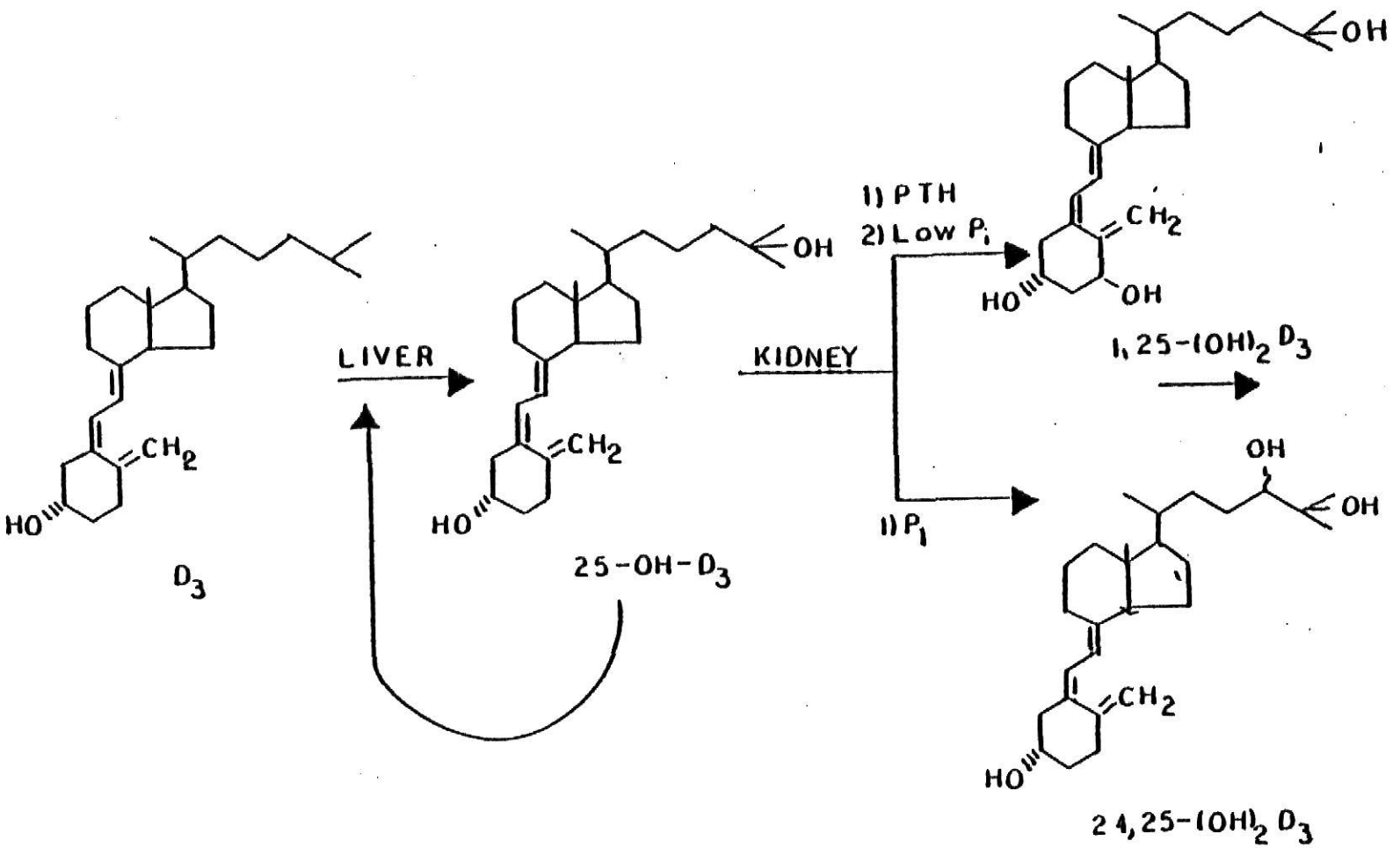


Fig. 2. The activation scheme of vitamin $D_3$ in animals and man (35).

cytosol receptor protein that binds either 25-OH-$D_3$ or the final hydroxylated form onto the receptor sites that are found on the nuclear chromatin. Isotope dilution is used to further distinguish vitamin D activity in the plasma.

Intestinal calcium transport is stimulated by 1,25-$(OH)_2D_3$ in the presence of a cytosol receptor protein (33). The mechanism of action resembles steroid hormonal action in its transfer to impure chromatin, which is highly specific for 1,25-$(OH)_2D_3$, other metabolites of vitamin $D_3$ and their analogs. Reynolds and co-workers concluded that the intestinal cytosol receptor protein bound 25-OH-$D_3$ and 1,25-$(OH)_2D_3$ with high affinity according to protein particle size.[3] A 6S protein bound 25-OH-$D_3$, while 1,25-$(OH)_2D_3$ bound to 3.0-3.7S receptor particles. Furthermore, they concluded that the administration of 1,25-$(OH)_2D_3$ in rats did not alter the subsequent binding of 25-OH-$D_3$ or 1,25-$(OH)_2D_3$. However, the administration of 25-OH-$D_3$ prevented in vitro binding to the 6S protein particle that is thought to occur commonly in the testes, spleen, kidney, liver, and gastric mucosa---but not in the serum.[3] Thus, 1,25-$(OH)_2D_3$ is not bound to the 6S protein that complexes with metabolites but acts as the initiator of the intestinal calcium transport by a mechanism other than induction of transport proteins.

---

[3]Reynolds, M.D., Knutson, J.C. & DeLuca, H.F. (1975) Binding of vitamin D3 metabolites to proteins in intestinal mucosa. Fed. Amer. Soc. Exp. Biol., Fed. Proc. 34, 893.(Abstract

Calcium moves from the mucosal to the serosal compartments in the presence of sodium and is transported actively by fluids. As discussed previously, vitamin $D_3$ is responsible for the movement of calcium into the mucosal cell, by activation of the ATPase enzyme in the phosphate transport system (34).

Activated vitamin D enhances intestinal uptake rates of strontium and calcium by conditioning the permeability of the intestinal mucosa for calcium and by dissociation of strontium complexes. Furthermore, it enhances mucosal calcium uptake by increasing the affinity of CaBP for calcium rather than strontium (36). Although vitamin D is the accelerator of the specific transport system for calcium, no one has established that it functions in the calcium transport process (33).

Strontium discrimination sites

Comar (37) suggested that the body selectively absorbs and retains calcium in preference to strontium. As calcium intake increases, strontium absorption decreases. The ability of the animal to discriminate between the two elements is believed to protect it against large body build-up of strontium. Enhanced synthesis of CaBP by activated vitamin $D_3$ limits the active transport of strontium across the mucosa. Preferential discrimination against strontium occurs before birth and during infancy, childhood, and adulthood. Specific sites of strontium discrimination are

located in cellular membranes where active transport is involved, such as in the gastrointestinal tract, kidney, mammary glands, placenta, and bone. Normally, the first discrimination site is the gastrointestinal system. As strontium enters the blood, additional discrimination occurs in other tissues.

In order to denote the discrimination in a physiological process, the "Strontium-Calcium Discrimination Factor" (DF) has been formulated (5). The factor is based on the relative discrimination that occurs in a process and the net effect on the Sr/Ca ratio of the sample. Discrimination factors are usually named to identify the specific physiological processes involved.

Strontium inhibition

Calcium homeostatic mechanisms, including the vitamin D endocrine system, control the production of $1,25\text{-}(OH)_2D_3$ (fig. 3) (33). Animals that ingest strontium tend to develop several physiological imbalances in this system. Omdahl and DeLuca (38), in reviewing earlier research, reported that stable strontium ingestion inhibited intestinal calcium absorption, depressed plasma calcium concentration, and promoted the development of rachitic bone lesions. The symptoms which resembled those resulting from vitamin D deficiency, were referred to as "strontium rickets" (38). Omdahl and DeLuca (39) produced this type of rickets in chicks with strontium inhibition. Strontium rickets differed from that caused by calcium or

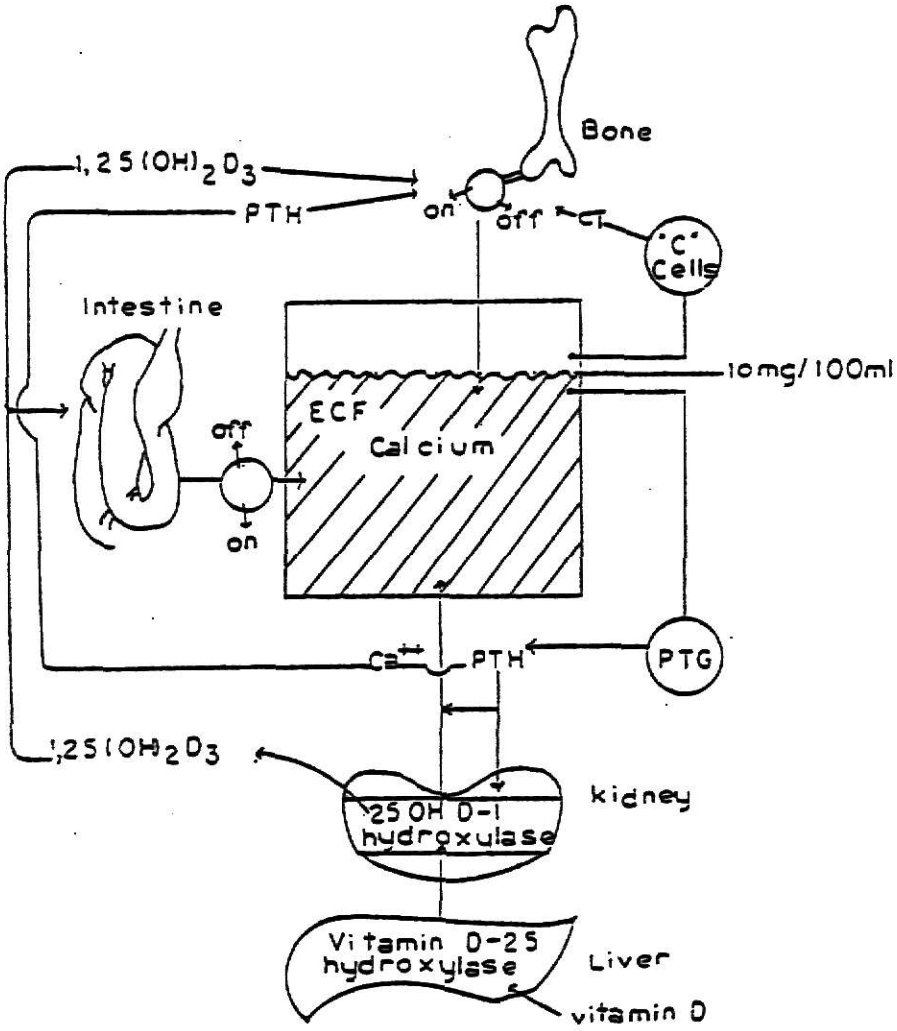


Fig.3 Diagrammatic representation of the calcium homeostatic mechanism involving the vitamin D endocrine system (33).

phosphorus deficiency in that supplementation with vitamin D had little effect. However, the return of normal bone structure occurred when chicks were fed a calcium-supplemented diet. Strontium acts antagonistically to calcium in bone mineralizatior and intestinal absorption. Replacement of dietary calcium with strontium results in diminished growth, improper bone mineralization, and inhibited intestinal calcium absorption (39). Strontium inhibits calcium transport by blocking vitamin D hydroxylation. The inhibition occurs during the synthesis of $1,25\text{-}(OH)_2D_3$ from $25\text{-}OH\text{-}D_3$ in the kidney mitochondria (39). Strontium rickets results from direct inhibition of calcificatior only; however, as it is detected in bones, the strontium inhibition of vitamin $D_3$-induced CaBP production is manifested. Then the intestinal calcium absorptive mechanism is terminated. The inhibition of calcium absorption and characteristic rachitic lesions which have been observed in animals fed strontium, are attributed to low intestinal concentration of $1,25\text{-}(OH)_2D_3$. Even with daily vitamin D supplements, chicks with strontium rickets remain "vitamin D-deficient" because of the metabolic block in the kidney mitochondria. Apparently, strontium acts like high serum calcium in the homeostatic control of $1,25\text{-}(OH)_2D_3$ synthesis, and blocks the calcium-sensitive feedback stimulation (38).

When dietary intake and/or absorption are not sufficient to meet calcium needs and calcium concentration decreases in

the body, strontium is absorbed as the best substitute. Major sites of deposition are in bone, teeth, and organ tissue. Strontium behavior in human beings resembles that in animals. Thus, 1,25-$(OH)_2D_3$ is necessary for the formation of CaBP and its discrimination against strontium in human beings. Regular consumption of strontium will decrease intestinal calcium absorption and CaBP production (40).

A later study by Omdahl showed that renal synthesis of 1,25-$(OH)_2D_3$ was suppressed in rats fed diets containing high levels of strontium or calcium. [4] Strontium inhibition was studied to determine if the parathyroid hormone (PTH) or calcitonin (CT) mediated the action. The results suggested that neither was required for the alteration of 25-OH-$D_3$ activity by strontium. In other studies (41), in which rats were fed high doses of vitamin D over long periods, the vitamin caused the strontium inhibition to disappear. It was suggested that strontium absorption increased because of the existence of only one absorption mechanism for the calcium and strontium cations.

A study by Rousselet and others (41) suggested that an overdose of vitamin D increased renal excretion of strontium, but produced no change in its plasma concentration. They suggested that excessive vitamin D removed some of the

---

[4] Omdahl, J.L. (1975) Cations and the modulation of renal 1,25-dihydroxyvitamin $D_3$ synthesis. (SPON: LeBaron, F.N.). Fed. Amer. Soc. Exp. Biol., Fed. Proc. 34, 893. (Abstract).

strontium, as well as calcium, from the bone complex. That is, low doses of vitamin D increase strontium bone fixation while high doses decrease it.

Inhibition that allows calcium substitution by strontium ions, does not distinguish between stable strontium and $^{90}Sr$. Following strontium absorption, a major portion is deposited in bones and teeth (24). Some deposition occurs in soft tissues. With absorption, the danger of strontium retention is enhanced and the characteristic bone malformations caused by changes in the crystal lattice of the skeleton develop.

Corradino et al. (40) fed chicks a diet containing 0.1% Ca and 2.62% Sr, and found that the calcium-binding activity in the intestinal mucosa declined rapidly as a result of strontium feeding, with inhibition being maximal within three days. The effects of dietary strontium on tibias of two-week old chicks can be observed in fig. 4 and 5. Strontium containing diets produced linear junctions between the hypertrophic cartilage and metaphyseal spongiosa. Following fourteen days of feeding, a flask-shaped deformity at the proximal end of the tibia occurred, and a mineralized defect was visible. The rapid feeding of the strontium diet blocked the process of cartilage calcification and endochondral osteogenesis. Additionally, the removal of hypertrophic cartilage and its replacement by osteoid cartilage was impeded markedly (40) Therefore, as calcium absorption from dietary sources is

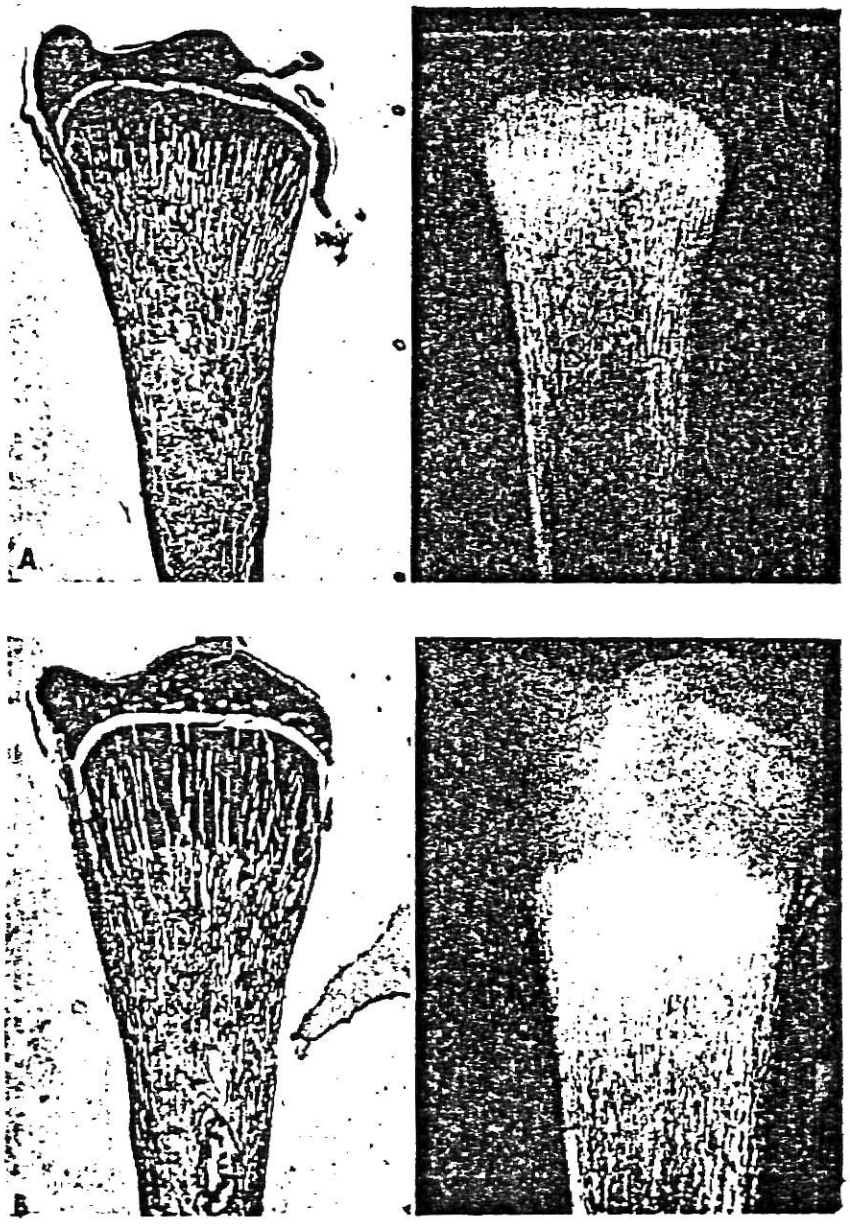


Fig. 4. Effect of dietary strontium on chick tibial histology and radiography X 5. (A) Normal chick, (B) chick after 3 days on the strontium diet (40).

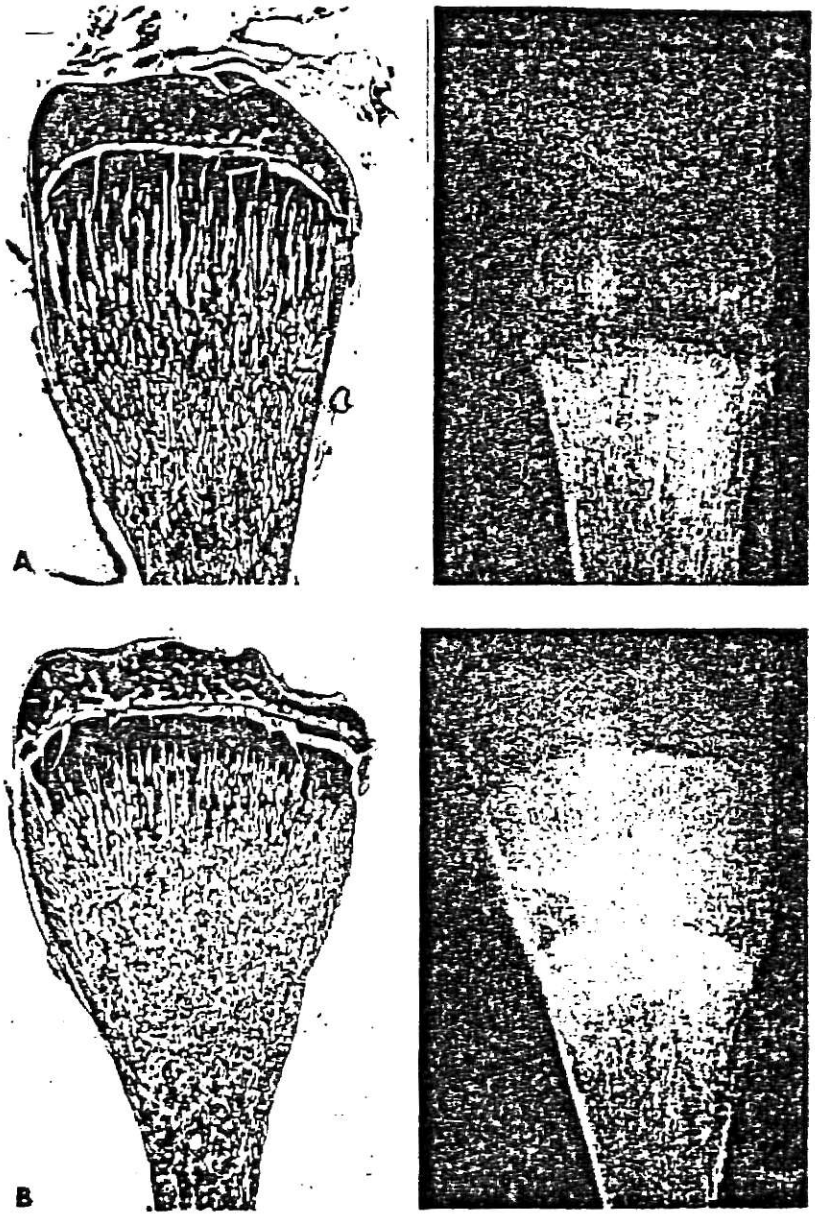


Fig. 5. Effect of dietary strontium on chick tibial histology X 5. (A) Chick after 7 days on the strontium diet, (B) chick after 14 days on strontium diet (50).

blocked through decreased 1,25-$(OH)_2D_3$ hydroxylation and reduced CaBP production, strontium substitution is enhanced and strontium is deposited instead of calcium.

## Metabolism

### Absorption

Approximately 20-70% of ingested strontium is absorbed (24). Fabrikant (42) observed that adult man has an average daily intake of 1.2 g of calcium, primarily from milk and milk products, however, only 0.3 g (25%) may be absorbed from the intestine. Most of the absorbed calcium is bound in bone tissue; smaller amounts are carried in fluids and deposited in soft tissue. The body reclaims calcium by its specialized resorption processes in the kidney.

Strontium occurs in food sources with calcium, with the highest accumulation in soil grown foods. The daily human intake of strontium is 1.6 mg based on a representative diet containing 1.2 g of calcium (42). Usually only one-third of the strontium consumed is absorbed, and the remainder is excreted in the urine and feces. Of that which is absorbed, about 15% is retained, with most of it deposited in the bone. Both stable and radioactive strontium are absorbed from the gastrointestinal wall to a limited extent. The intestinal absorption of calcium exceeds that of strontium by a factor of 2 to 4. About 50% of the absorbed calcium and strontium are

bound by CaBP in the intestinal tract. Strontium, like calcium is deposited primarily in the mineral phase of bone (43).

Strontium absorption is influenced by the vitamin D status of the individual and the presence of other substances in the diet that tend to promote or depress absorption. Vitamin D affects absorption of calcium and strontium by (43):

1. Increasing passage across the luminal surface of the intestinal wall
2. Increasing intracellular turnover
3. Enhancing the total flux and mucosal tissue uptake of strontium and calcium.

The magnitude of absorption is regulated by pH and the stimulation of mucosal cell uptake, which is not specific for calcium and strontium. CaBP activity is dependent upon pH and ionic strength and is not decreased by treatment with ethylenediaminetetraacetic acid (EDTA) or iodoacetate (36). CaBP binds one atom of calcium to one protein binding molecule and is similar to sulfate-bacterial protein transport.

Vitamin $D_3$ induces the CaBP formation in the intestinal mucosa, and thus enhances the mucosal uptake of strontium and calcium from the lumen and only relative specificity occurs between them. An essential characteristic of the CaBP macromolecules is their ability to complex with the substrate being translocated, and constitutes the basis for assay of the speculated carriers (36). The carriers are present in the brush border, and are activated by vitamin D, thus causing a

resynthesis or reorganization of protein in the membrane of the microvilli. CaBP causes the release of calcium from the mitochondria of intestinal mucosa cells. Vitamin D accelerates the specific transport system, and when a deficiency exists, the efficiency of the system declines. Restriction of dietary calcium increases calcium affinity for the carrier and the capacity of the transport process. Vitamin D increases the incorporation of leucine into CaBP prior to absorption. Increases in the mucosal tissue CaBP content parallel the rate of calcium transport. Vitamin D acts as a transcriptional device in order for CaBP to mediate calcium transport (31). CaBP is responsible for the translocation of calcium and related cations across the intestinal epithelium. The relative binding affinity of CaBP for alkaline earths and the degree of absorption in the intestine follow the same order as the periodic rating, calcium being greater than strontium. Vitamin D facilitates the absorption of calcium ions but will influence movement of other calcium-like ions also. Calcium is absorbed immediately upon contact with the mucosa, whereas strontium moves primarily by slower, passive diffusion.

Acute radiostrontium exposure occurs in the ileum, duodenum, and jejunum. The slowness of strontium movement in the ileum accounts for the organ being the primary site of absorption. However, the duodenum and jejunum can absorb

strontium at a rate 4-5 times greater than that of the ileum. The colon and stomach may participate to a lesser extent as absorption sites (44). Depressed absorption of calcium occurs when high intakes of strontium inhibit the conversion of 25-OH-$D_3$ to 1,25-$(OH)_2D_3$ by the kidney enzymes and hence formation of calcium-binding proteins (CaBP) (45).

Amino acids, carbohydrates, dietary calcium and phosphate concentrations, radiation threat, age, oxalates and phytates affect strontium absorption. Tested in rats, 18 amino acids, lysine and arginine almost doubled the strontium and calcium absorption, while tryptophan, leucine, and aspartic acid produced a lower-magnitude of increase, and the remaining amino acids had little or no effect (5).

Carbohydrates including cellobiose, sorbose, ribose, xylose, raffinose, melibiose, glucosamine, mannitol, and sorbitol, and especially lactose, increased strontium absorption (5). Their effectiveness was correlated with their length of time in the gastrointestinal tract. Glucose, galactose, fructose, and sucrose did not affect absorption. Radioactivity, lysine, lactose, age and calcium intake levels increased strontium absorption while oxalates and phytates depressed it.

**Transport**

Carr (46) has proposed a three compartment model to describe the nature of strontium activity and movement. Following absorption from the gut, or the first compartment, a loss of strontium from the pool by urinary and endogenous fecal excretion occurs. The second compartment, the soft tissue and the bone surfaces, equilibrates with the first compartment within two weeks. The third compartment, or the bone complex, is in equilibrium with the other two.

Strontium is transported against a concentration gradient from the serosa to the mucosa. Strontium is restricted to movement from the lumen to the plasma by passive diffusion. In the ileum the movement of strontium from the plasma to the lumen may be facilitated by active transport, although that mechanism operates in favor of calcium absorption. The absorbed cations enter the circulatory systems through the lymph vessels and blood capillaries. Strontium is transported by passive diffusion, where the movement is through water-filled pores in the membrane. The lipoprotein membrane interacts with the substances to be transported and facilitates their passage by becoming temporarily soluble. Diffusion is slowed by the number of available carriers and the balance between solutes on both sides of the barrier.

Tissue distribution and retention rates

The major portion of body strontium deposits are in the target tissues of 1,25-$(OH)_2D_3$ action: the intestine, bone, and kidney. Tipton and Cook (47) found strontium concentrations (ppm in dry tissues) for adult human tissues to be: adrenal, 0.06; muscle, 0.07; liver, 0.10; brain, 0.12; heart, 0.15; kidney, 0.035; and lung, 0.50. The relatively high quantity in lung tissue is attributed to inhalation of strontium-contaminated air.

Strontium has a greater affinity for bone mass than for other tissue. Hodges et al. (48) reported a concentration of strontium of 0.016% in fetal bone while bone of human adults contained 0.024%. Gedalia et al. (49) found that the strontium content of ashed mandibles and teeth of stillborn human fetuses at various developmental stages reflected differences in the ingestion of strontium-contaminated drinking water by the mothers. The study included mothers who lived in three undisclosed regional areas during their pregnancy terms. The drinking water contained strontium (Sr) and fluoride (F) in the following amounts: Region A: Sr, 1.12 ppm; F, 0.1 ppm; Region B: Sr, 1.07 ppm; F, 0.55 ppm; Region C: Sr, 1.53 ppm; F, 0.6-1.0 ppm. In all cases, lower levels of strontium were found in mandibles of nine-month old stillborn fetuses than in adults living in the same region. The lower strontium values were attributed to the rate of growth at the time of

examination. Although some strontium discrimination occurred during fetal development, strontium deposits were found in the stillborn fetuses.

Strontium is laid down in tooth enamel in substitution for calcium during formation. In a comparative study, strontium concentration in tooth enamel was 145.8 ± 41.0 ppm in third year molars prior to eruption and 138.8 ± 38.0 ppm following eruption. There was no significant difference in values for individuals living in the same region (49).

A more recent study (50) of trace element concentrations, including strontium, in preindustrial and contemporary Hopi Indian populations has been reported. Deciduous teeth from 17th century Hopi tribes contained 477 ± 86 ppm strontium, a four-fold higher level than found in contemporary Hopi or California children. Strontium has been found in high concentrations in some traditional Hopi cornmeal foods.

Strontium enters bone with calcium by two processes of exchange. The first process is rapid and occurs within a few hours after ingestion. Strontium is somewhat susceptible to removal by substances that deplete the exchangeable sites in bone. The second exchange process is that of accretion. In new bone formation, strontium is deposited in the crystal lattice of the skeleton until resorption sites are filled during normal bone growth. Once strontium is bound to the non-exchangeable portion of bone, depletion of skeletal

bound mineral cannot occur without massive withdrawal. Calcium and strontium are believed to be deposited in the skeleton in the form of hydroxyapatites and carbonates in a complex system of crystal lattices. The loss of strontium from bones could result from an exchange mechanism whereby strontium is removed from the surfaces of crystals of bone mineral, and is replaced by calcium (51).

Christensen et al. (52) studied the levels of $^{90}Sr$ in bones of Norwegians, during the period of 1956-1972, and found a single high value of 24.6 pCi $^{90}Sr$/g Ca. In the early 1960's, a mean contamination value of 2 pCi Sr/g Ca was found in a group of stillborn infants, while levels of 4.6 to 11.0 pCi Sr/g Ca were observed in infants. In 1972, 4.0 pCi Sr/g Ca were found in infants, and children and adolescents had a high value of 15.8 pCi Sr/g Ca. A mean contamination value of 10.9 pCi Sr/g Ca was observed in adults in 1970.

In man, an absorbed dose of 1 μrad/day in new bone occurs when the daily intake of $^{90}Sr$ is 1 pCi (27). Nonuniformity of labeled bone mineral after short exposure, and differences in growth, turnover patterns and geometric structure of bone mineral with respect to adjacent cells, tended to decrease the estimate. By consuming about 1 liter of milk per day, ( approximately 1 g of calcium or 10 pCi $^{90}Sr$/day), up to 10 μrads of exposure/day to the sensitive cells of the bone and marrow could be tolerated (27).

Retention is calculated as the difference between the total quantity consumed and the total output in urine and feces (51). Marshall's law expresses the biological retention (R) of alkaline earth elements in (t) days after injection, (53):

$$R=E^{b}(t+E)^{-b}$$

where (b) and (E) are constants. Retention is presumed to follow a single exponent. Muller and Thomas (53) used this formula to indicate the biological retention per unit injection of an absorbed strontium dose in adult humans. Once radioactive strontium is absorbed into the circulating blood plasma it is recycled through the intestine and kidney with slight losses in both feces and urine.

**Response to phosphorus**

**The absorption, excretion, and retention of strontium are controlled effectively by dietary phosphorus intake.** Phosphorus controls the deposition of minerals in the skeleton and determines the quantity and quality of bone calcification after birth (51). Low amounts of phosphorus in the diet and low serum concentrations limit the preferential deposition of calcium in the skeleton (51). Phosphorus supplementation of the diet decreases strontium excretion in urine. When the diet and serum are extremely low in phosphorus, the kidney reabsorbs almost all the phosphorus in the filtrate. With further phosphorus depletion, strontium is removed from the bone mass and excreted. Removal from bones occurs in an

exchange mechanism whereby strontium is lost from bone surfaces, and calcium is substituted. Then strontium concentration is increased in body fluids, and final removal occurs by renal recycling action. Phosphates induce remodeling of bone salts and redepositing of calcium from serum and dietary sources (51). Increased phosphorus intake will increase calcium and strontium absorption and decrease bone quality. When reduced levels of phosphorus occur in the blood, calcium is deposited in bone mass to a greater extent than strontium, thereby increasing bone quality.

Inorganic phosphate (Pi) level in the cell is an important regulator of 1-hydroxylase activity and mineral deposition. Production of 1-hydroxylation which also is regulated by serum calcium and parathyroid hormone, is stimulated by phosphate deprivation in animals (33). As cellular phosphate concentration levels rise, synthesis of 24, 25-$(OH)_2D_3$ occurs, whereas low phosphate levels favor production of 1,25-$(OH)_2D_3$. Furthermore, 1,25-$(OH)_2D_3$ is required for 24-hydroxylase monitoring and renal cell change, permitting regulation by parathyroid hormone and inorganic phosphate (33). Thus, low cellular phosphate concentration favors 1,25-$(OH)_2D_3$ production for high quality bone mineralization.

**Excretion rates**

Strontium and calcium in plasma are present in three forms: protein-bound, complexed, and free state. The kidney has the most significant role in elimination of strontium from the plasma. Through the kidney's ability to alter the ionic concentration in the blood and maintain normal acid-base balance, urinary excretion of ingested or parenterally administered strontium occurs rapidly, with mamimum excretion following consumption. The urinary excretion rate is directly proportional to the plasma concentration; it is independent of the stable strontium level up to 100-fold or more concentrations (5). As the fluid passes through the glomerulus, and ultrafiltration of serum occurs, only ionized calcium and strontium and those ions associated with small molecular weight anions are capable of passing across the glomerular membrane. About 99.5% of the filtered calcium is reabsorbed in the proximal tubule by an active process, while strontium reabsorption is slightly less, about 98.5% under normal conditions. Strontium excretion in urine exceeds that for calcium by a factor of 2 to 3 (43).

Urinary excretion rates are expressed conventionally in terms of clearances, clearance ratios of strontium to calcium or $OR_{urine/plasma}$. Commonly, Sr/Ca ratios in the urine are 3-10 times greater than in the plasma (5). Difficulties in assessing the OR urinary values arise from

the complexed states in which strontium and calcium pass through the glomerular membrane into the ultrafiltrate. Strontium is bound less ofter than calcium to plasma proteins, but only slightly observable renal discrimination is detected. The free ions of strontium are absorbed from the glomerular ultrafiltrate in the renal tubules. The difference in reabsorption rates of calcium and strontium is the major basis of renal discrimination. No discrimination occurs at the glomerular filtration site; there is no distinction in ion size of strontium and calcium.

Urinary assay is the most direct method known for estimation of recent contamination with $^{90}Sr$ in animals (5). There are many factors that influence the relative renal clearance of calcium and strontium expressed as $OR_{urine/plasma}$. Normal dietary conditions are relatively constant for the species; thus, the $OR_{urine/diet}$ is useful in assaying current levels of $^{90}Sr$ intake in human populations. Comar (37) states that certain physiological processes affect strontium retention and the extent to which urine and blood levels of strontium vary. In summary, preferential absorption is for calcium and preferential urinary excretion is for strontium, especially when plasma and urinary values remain at steady state, although diseased or healthy conditions may cause alterations.

Placental transport

During the perinatal period, calcium and strontium are transferred across the placenta; however calcium is preferred. Mineral transfer, especially calcium, occurs from maternal to fetal blood by active transport and concentration gradient. In animal studies (54), placental transfer of strontium was about one-half that of calcium. The strontium and calcium deposited in fetal bone was from two sources: the diet, and the maternal skeleton. Major discrimination favoring calcium occurred at the placental barrier from mother to fetus, with little or no differential movement from fetus to mother. Overall discrimination ratios of Sr/Ca from diet resulted from absorption, urinary excretion, and placental transfer. In overall fetal development, calcium was used preferentially over strontium from the diet by a factor of about five, and from stored body pools by a factor of 1.5. Radiostrontium moved easily in either direction across the placental membrane, and no specific directional discriminatory mechanism affected the passage.

Another route of strontium and calcium entry into the fetus was through the fetal consumption of large quantities of amniotic fluid (54). Strontium and other minerals were absorbed through the wall of the fetal gastrointestinal tract.

Fetal urine was excreted into the amniotic cavity and reswallowed. The amniotic fluid contained low concentrations of magnesium, phosphorus, and sodium, and lower concentrations of calcium and potassium. Strontium was found in the highest concentration. Apparently the fetal kidney, as in postnatal life, can discriminate against strontium in the reabsorptive process, and it excretes slightly more strontium than calcium in the urine.

Meconium, or the dark green sticky mass in the intestine of the full term human fetus, contained high concentrations of minerals, especially strontium (55). Usually, the intestine of the fetus is filled with this material before birth, and it is passes out during the first or second day ofter birth. The minerals in the meconium arise from abraded cells, high in magnesium, intestinal secretions, and imbedded amniotic fluid. Analysis of the meconium indicated that relatively more calcium than strontium was absorbed from the fetal intestinal tract than was eliminated. Maternal and fetal discrimination between calcium and strontium represents an additional protective factor for the developing fetus (54). Fetal Sr/Ca content is governed by the strontium and calcium ingestion by the mother, shortly before and during gestation (54).

Mammary transport in animal and man

Following absorption and entry into the circulating fluids of the body, radiostrontium nuclide can be found in milk of lactating animals. Generally, milk-secreted mineral elements enter from the blood plasma, and the concentration in milk differs from the concentration in the plasma. A maximum concentration of $^{90}Sr$ in dairy cow milk is reached at about 24-48 hours after the ingestion of a single dose and approximates 0.02% of the dosage level per liter of milk (56). The total amount of ingested $^{90}Sr$ appearing in milk is highly variable, but it has been reported to range from 0.3-4.0% of the dose for cows, goats, and man (56). The percentage of ingested radioactive strontium secreted per liter of milk, is more than 10 times higher for goats than for cows, primarily because goats concentrate a much larger proportion of dietary calcium in their milk than cows.

In milk, about 70 to 80% of the calcium is bound to casein. This is in contrast to blood where more calcium than strontium is bound to casein. The amounts of ingested strontium is reflected in the milk but the calcium concentration in milk is essentially constant regardless of dietary intake.

Discrimination in the passage of strontium and calcium from the diet to milk is dependent upon phosphate levels. The mammary glands tend to accumulate strontium in portions of the caseinate colloid and in small non-exchangeable

forms. The strontium and calcium in milk are derived largely from those minerals in the diet, with a small contribution from skeletal reserves (56). Discrimination occurs unidirectionally in the preferential movement of calcium over strontium from blood to milk, which is similar to placental movement.

Movement of strontium in mammary tissues of human beings is controlled during its passage from blood to milk by the ability of the mammary cells to discriminate between strontium and calcium. Mammary tissues secrete about one-half as much strontium as calcium into milk. This discrimination is similar to that which occurs in the intestine and kidney. The Sr/Ca level found in breast milk is one-tenth that found in the mothers diet. Mammary discrimination is influenced by the consumption of high or low calcium-containing diets, and especially by alteration of the dietary Ca/P ratio.

**The ratio of Sr/Ca in human breast milk is similar to that in the infant's bones at birth. Preferential movement of calcium across the placenta as compared to strontium accounts for this rate of deposition.**

**Stable strontium toxicity**

The major interest in strontium toxicity caused by excessive retention in bone is the production of strontium rickets. Bartley and Reber (57) examined the toxic effects of stable strontium in young pigs. Signs of strontium

toxicity included (1) decreased activity and (2) slowed eating time, which was followed by incoordination and weakness in the rear limbs, humped backs and braced legs. As the induced rickets progressed, the animals were unable to stand unaided, and finally all four limbs became paralyzed. Closer examination of the bones indicated beading of the ribs and bending of long bones, deformities of the epiphyseal plates and joint surfaces, and decrease in the average lengths of the femurs. Their observations were similar to those of Omdahl and DeLuca (39), who produced rachitogenic activity in chicks by dietary strontium inhibition.

During metabolic balance studies of strontium in adult men, Warren and Spencer (58) found that strontium used for the treatment of osteoporosis resulted in transitory retention of strontium, mainly during the period of administration. There is now evidence of toxicity with long term administration of large amounts of stable strontium in man. Strontium retention and toxicity are more prevalent in the young, especially when calcium intakes are low (59).

The ability of strontium to block intestinal absorption of calcium is of great concern for the very young, in whom less strontium is excreted and the Sr/Ca discriminatory steady state controls are not well established. Infants are very susceptible to absorption of strontium, depending on its source and concentration (59).

## Radioactive strontium toxicity

Radiostrontium, as well as stable strontium, has an affinity for bone. Radioactive strontium in the atmosphere can contaminate the soil and subsequently enter dairy products, vegetables, cereals and thus bread. The isotope gains ready access to the gastrointestinal mucosal surface, which may show very little discrimination from calcium. Radiostrontium is absorbed readily into the blood plasma, and recycled through the intestine and kidney with some loss in the feces and urine. Radiostrontium retention is particularly hazardous, because radiation accumulates in bones where red blood cells are synthesized. The hazard is more acute in children, who have a greater intake of dairy products, particularly milk, and a variable steady state Sr/Ca ratio attributable to their sporadic growth.

Since 1957, following the development and explosion of very large nuclear weapons, $^{90}Sr$ has entered the biosphere as fallout, contaminating man, water, and foodstuffs. Several radionuclides, especially $^{90}Sr$, have great affinity for osseous tissues. Two types of bone-seeking radionuclides exist; the actinide elements—thorium-228 or radiothorium and plutonium-239, and the alkaline earth elements such as radium and strontium. Strontium radionuclides deposit in sites identical to those of calcium in bone. The deposits or hot spots are concentrated in rapidily calcifying bone

matrix beneath osteoblastic surfaces and osteoids. The growing surfaces of the pre-existing old bone in areas of lighter, more uniform concentration are called the diffuse components (42). Hot spots form only where active bone growth is occurring. The same active apposition of bone, which is essential for strontium hot spot concentration, is the process that buries the hot spots promptly within less radioactive bone (42). Radioactive strontium has been found to be nonuniformly deposited in bone, making estimation of dose from the radiation very difficult to monitor.

Radioactive strontium is passed to human beings primarily through ingestion of milk. The concentration in milk reflects both the rate of fallout and the total amount of $^{90}Sr$ deposited in the earth's surface. Retained $^{90}Sr$ affects bone, teeth and blood-forming tissues in the bone marrow. Bone is a complex tissue with cells growing on the surface (42). Tumors tend to arise from the osteogenic tissue on bone surfaces while the bone is growing, quiescent, or resorbing. They are found on the trabecular bone, in the Haversian canals or on periosteal or endosteal surfaces (42). The high carcinogenicity of repeated intake of bone-seeking radionuclides may be related to protracted doses (prolonged over extended periods) and the irradiation of osteoblastic tissue (42). Maximum tumor induction occurs even

with a low dose of $^{90}Sr$, a beta emitter. The beta emitters have a damping effect (the steady decrease of a specific form of energy) on tumor production as the amount of isotope exceeds the optimum carcinogenic radiation level. Most tumors are produced by radiation doses that induce the greatest amount of neoplastic change while destroying the smallest number of potentially neoplastic cells (42).

Radioactive strontium beta emitters illustrate the effects of differences in radiation energy upon carcinogenic effectiveness. Radioactive strontium decays rapidly to a higher energy $^{90}Y$ daughter, and their combined energy is ten times that of $^{45}Ca$. Ten times the dose of $^{90}Y$ is required for tumor induction to equal that produced by $^{90}Sr$ (42). The potency of $^{90}Sr$ results from its higher energy $^{90}Y$ daughter, although the contribution to $^{90}Sr$ carcinogenicity is negligible. Maximum tumor induction appears to occur with the bone-seeking beta emitters $^{90}Sr$ (42).

Thorne and Vannart (60) suggested that $^{90}Sr$ predisposes man to diseases of the skeleton and bone marrow. Current predicted risk of hereditary disease from genetic mutation from exposure is one percent. The risk estimates apply to exposure early in life but are overestimates of the true risk; i.e., those induced later in life, a long time after exposure. Rem units, roentgen equivalents/man, are the designated dose levels used, and indicate the absorbed dose of ionizing

radiation times relative biological effect. Leukemia is the predominate risk from exposure to $^{90}Sr$, and accordingly, is of the greatest concern. The risk of developing myeloid leukemias is much higher than that of developing osteosarcoma lesions. Leukemia can result from high levels of ingested $^{90}Sr$ (60). The risk is related linearily to dose, and the organ or tissue risk is proportional to the resulting average total dose of $^{90}Sr$ received by that tissue before exposure. According to Maximum Permissible Annual Intake, (MPAI), levels of $^{90}Sr$ up to 0.37 uCi are safe (60).

Radioactive tracer studies

In the mid 1950's, studies were started in which tracer amounts of radionuclides of strontium were administered to patients, or relatively high levels of stable strontium were administered to normal individuals. Radioactive $^{85}Sr$ or $^{87m}Sr$, and $^{45}Ca$ are useful analytical tools for identifying movement and metabolism of strontium. Animal studies, using radionuclide tracers, have helped to establish the physiological behavior of the alkaline earth elements. A major advantage of radionuclide investigative biology has been the development of diagnostic and therapeutic techniques for protracted internal radiation exposure of human tissues. Human studies, in which bone-seeking internal emitters have been employed, have been hampered because of the problems related to dose distribution throughout the body; the heterogeneous composition

of the various energies from the radiations of different linear energy transfer; and the variation among subjects in the rate of excretion of the radionuclides and daughter products. Evidence indicates that during periods of protracted radiation exposure the rapid renewal of cell populations, associated with bone-osteoblasts, hemopoietic tissues, and cellular linings of periosteal and endosteal membranes are subject to cellular radiation damage, depopulation and formation of damaged tissues (42).

Metabolic pathways of radionuclides and their compounds are determined by retention studies during oral intake, intravenous administration, inhalation, and external absorption, such as through the skin. A radionuclide-containing compound, which enters the body by one of the pathways, is transported across body membranes, fixed in tissues or eventually eliminated. Elimination can occur by exhalation or in sweat, urine and feces.

## Strontium Accumulation in Human Infants and Adults

Calcium and strontium compete for biological transport and deposition during all phases of development and at all ages. Monitoring at the various stages provides an accurate determination of strontium accumulation and a better understanding of its metabolic activity.

## Effects of dietary intake on strontium tissue level

### Infants

Infants are very susceptible to strontium absorption depending on the strontium source and concentration. Babies are born with strontium in their skeletal system. The average calcium level in the full term baby at birth is about 28 grams, and the amount of strontium is just over 5 milligrams (51). The amount of initial strontium deposits can be determined by analyzing the infants' deciduous teeth. The amount of strontium in different milks affects absorption and excretion of strontium in the body of infants. Commercial cows' milk preparations used by most hospitals contain six times more strontium than human milk (51). Commercial milk formulas contain 4 and 5 times more of calcium and phosphorus, respectively, than does breast milk (51). The level of strontium in ashed human milk was 10 ppm (61). When infants are fed cows' milk with a strontium concentration much greater than that found in human milk, they are less protected from strontium inhibitory effects than are breast-fed infants.

#### A. Breast-fed

Breast milk contains much less phosphorus than cows' milk

formulas. When breast-fed babies were fed phosphate supplements, they tended to excrete less strontium in the urine than unsupplemented breast-fed infants (51). The average excretion of those receiving phosphate supplements was similar to that of bottle-fed infants.

In another study of absorption, excretion, and retention of strontium in breast-fed infants, high urinary excretion of strontium and calcium of breast-fed babies was reduced by the administration of phosphorus. The rate of postpartum growth was governed by phosphorus. When low levels of phosphorus occurred in the blood, calcium was deposited in the bone mass, preferentially (33).

The ratio of Sr/Ca in breast milk is similar to that in the baby's bones at birth. Widdowson et al. (51) found that breast-fed babies tended to be in positive calcium balance and strongly negative strontium balance; that is, more strontium was present in their urine and feces than in their food. Apparently the increased excretion was caused by the mobilization of strontium from the bone salts deposited before birth (51).

There is preferential calcium absorption over strontium from the digestive tract. In breast-fed infants, strontium elimination exceeds that of bottle-fed infants and older children (62). The strontium elimination ratio is similar to adults. The intestinal glands of young babies secrete

strontium into their digestive juices in relatively large amounts, especially if breast-fed. The strontium containing juices are in turn eliminated through the feces.

When infants are breast-fed, they continue to lose strontium at the rate of 20 μg/kg body weight per day, and in less than 3 months no strontium remains (62). The rate of loss tends to decline as the strontium body level falls. Furthermore, despite the lower intake and absorption of calcium, magnesium, and strontium from breast milk, greater amounts of strontium are excreted in the urine by breast-fed than by bottle-fed infants.

B. Bottle-fed

Infants who are fed formulas based on cows' milk have Sr/Ca ratios in their diets that resemble those of their mothers (62). Bottle-fed babies tend to be in positive strontium balance. Only 7-10% of absorbed strontium is excreted, as compared to 50% strontium excretion by breast-fed infants. The consumption rate of commercial formulas having higher concentrations of strontium, calcium and phosphorus determines the extent to which strontium is retained or eliminated. Bottle-fed infants show a slightly higher fecal content of strontium than found in their food intake. Also infants fed commercial cows' milk preparation double their body strontium content over a period of one month, and have an increased calcium absorption rate of 17% (51).

Adults

The adult body always tends to discriminate against strontium in favor of calcium (5). The ratio of strontium to calcium eliminated in the urine is higher than that found in the body as a whole. Adults on a uniform diet of stable strontium and calcium reflect a steady state calcium homeostasis throughout the body. In adult man the preferential urinary excretion of strontium is controlled by this homeostasis system. Adult man absorbs 20-40% of ingested strontium and 40-80% of ingested calcium (63). For adult man and other mammals, $OR_{body/diet}$ averages are about 0.25. Skeletons of adult man formed entirely from a diet of $^{90}Sr/Ca$ reflect values one-fourth the dietary ratio; the total body burden estimate is a reflection of the total calcium available.

Factors affecting strontium retention and excretion rates

Strontium may enter many metabolic pathways in transient concentrations. Radioisotopes, after incorporation, become inflexibly bound to individual organs and skeletal mass. Therefore, the investigation of certain factors of external influence that are capable of upsetting radioactive equilibrium activity are of particular interest.

Age

Of the many physiological factors that affect the total amount of absorption of calcium and strontium from the digestive tract, the most important is the age of the animal. Absorption of both minerals decreases as the animal grows older, however absorption of dietary calcium always exceeds that of strontium. Infants from 2-9 months of age show about the same ability to absorb calcium and strontium as adults, but not the extensive discrimination pattern against strontium (44). Children from 4-14 years of age follow the adult pattern of absorption of calcium and strontium, and their discrimination ability increases with age.

Kidman et al. (59) identified factors in rabbits that affect strontium absorption and metabolism, including age, amount of calcium in the diet, and increased demands for calcium, such as during pregnancy and lactation. Their studies showed that most of the total body strontium was found in the skeletal structure, and retention was affected most by age and diet. Rabbits fed low calcium diets versus those on high calcium diets, showed greater strontium retention, greater fecal excretion of strontium than urinary excretion, and greater excretion in young animals than in old.

Sex

Stevenson (63) observed the influence of age and sex on the behavior and distribution of $^{90}Sr$ and $^{90}Y$ in albino rats after administration of solutions of those radioisotopes. The ratio of yttrium/strontium, or Q, was found to be proportional to age, and it was significantly higher for female animals than for males. Both sex and age acted by increasing the radioactive burden of the bones, and the increase was substantial in female animals. As members of the mammalian species approach sexual maturity, the concentration of certain minerals in the body is altered, with distinct sexual differences. Such sex differences in body composition are well established for calcium, phosphorus, and iron. The uptake of those elements by different organs and tissues is the same in young animals of both sexes until sexual maturity. During adulthood, females tend to have higher concentrations of those elements than males. Similar sex discrimination and distribution have been shown in strontium metabolism.

During growth, the available or active skeleton areas permit free ion diffusion, and skeletal remodeling is variable with age and species (63). After skeletal growth has ceased in animals, the rate of bone resorption exceeds that of formation, resulting gradually in a condition of physiological osteoporosis. The greater availability of

resorption sites in aged animals facilitates better incorporation of yttrium (63). The change in Y/Sr ratio may be influenced by sex and sex hormones. Estrogen may promote transport of yttrium to the ultimate site of deposition in bones of females (63). The combined effect of sex and increasing age is attributed to differences in absolute strontium uptake, physiological status, and growth hormone levels, or sex differences that facilitate absolute uptake of yttrium (63).

Calcium and phosphorus in diet

Increased dietary Ca/P ratios interfere with absorption of phosphorus, and in turn high P/Ca ratios interfere with calcium absorption. But, high levels of calcium when combined with low levels of phosphorus and inadequate vitamin D result in both depressed phosphorus utilization and depressed calcium retention. Widdowson et al. (55) found that feeding excess phophates to breast-fed infants reduced the absorption of calcium and magnesium (Mg) from the intestines.

Nordio et al. (64) observed conditions of chronic hypocalcemia, tetany, and convulsions in a seven month old boy following three years of primary magnesium malabsorption, swollen mitochondria of the intestinal mucosa cells, and high magnesium values in sweat. Further examination of Mg, Ca, and Sr concentrations of that chilk and other children fed

high and low Mg diets indicated the following: more than one transfer system existed for those cations in the intestine; and in magnesium malabsorption, simple diffusion of Mg and Sr was impaired, and the calcium serum level increased. Although the influence of Mg on Ca-P homeostasis was not clearly defined, a resistance to parathyroid hormone and vitamin D in Mg deficiency was observed.

Widdowson et al. (55) reported that large amounts of magnesium increased urinary excretion of calcium in breast-fed infants; by elevating the phosphorus intake; the effect of Mg was counteracted and urinary excretion levels of calcium returned to normal. Increased skeletal Ca and Mg retention rates showed that the amount of phosphorus in milk regulated quality of bone calcification and growth of soft tissues at an early age. Normal levels of phosphate promoted absorption of calcium and magnesium, but reduced it if fed in excess. Thus, growth and remodeling of bone were affected by the phosphate concentration in the blood.

Normally as calcium intake increases, strontium absorption decreases. Escanero et al. (66), using a duodenal perfusion technique, studied the effect of calcium concentration and metabolites of vitamin $D_3$ on intestinal strontium transport in vitamin D deficient rats. When the calcium concentration was increased, passive absorption of strontium was decreased, Vitamin $D_3$ and its derivatives increased intestinal strontium transport significantly, and this increment was not modified

by calcium. In their experiment, calcium was competitive with strontium only in passive absorption.

Demands for calcium by the body

Strontium absorption and retention are affected by the demands for calcium by the body, and the body's ability to meet calcium needs (31). Homeostatic calcium control including balanced plasma calcium concentration is evoked by adverse physiological events and demands as they occur in the body. For example, as physiological demands for calcium increase, skeleton-plasma pool concentrations decrease. The intestinal lining is capable of determining within wide limits the amounts of calcium allowed to enter the storage pool from the lumen. This maintenance function occurs during growth particularly, and during adult life. The parathyroid gland, functioning in conjunction with phosphorus levels in the serum, regulates the change in plasma concentration of calcium ions by (1) stimulating calcium mobilization from the skeletal reservoirs, (2) renal control of urinary calcium excretion, and (3) the resorptive capacity of bone material (31).

During pregnancy and lactation, calcium needs are increased to facilitate the formation of fetal bone and teeth, and for milk production. Furthermore, calcium is necessary for the regulation of tissue development and fluid movement. Strontium is unable to perform these functions. The calcification of the human fetus requires 35g of calcium at maximum, and a drain

of about 3.5% occurs unless adequate calcium is provided in the diet (31). Lactation imposes a great calcium demand on the mother. As calcium need increases, chances for strontium entrance and deposition increase also, especially when calcium intake is too low to meet needs.

## Control of Strontium Retention in Animals

A major concern in strontium metabolism is the ability to control its retention in the body. Strontium inhibition of calcium must be considered, but more importantly, the accumulation of stable and radioactive strontium must be prevented. Radioactive $^{90}Sr$ and its high-yielding fission product $^{90}Y$, predispose man and animal to two forms of carcinoma, leukemia and osteosarcoma. Onset of either of those diseases may follow exposure to radioactive $^{90}Sr$ (60). As discussed earlier, young animals tend to retain $^{90}Sr$ while older animals excrete it (59).

The influence of dietary factors, including calcium, phosphorus, lactose, lysine and vitamin D, on retention has been discussed. Other methods of control, such as substitution by stable strontium and use of extracts from plants and structural analogs are under investigation.

### Strontium substitution

#### Substitution of stable strontium for radioactive

derivatives in a biological system has been suggested as a method for reducing the concentration of strontium in bone. Most studies have shown that administration of stable strontium to animals had no effect on radiostrontium absorption and retention, whereas other have reported decreased absorption on the material (66). In general, animal study results are the same, whether radioactive strontium is administered orally, intravenously or intraperitoneally.

In human stable strontium substitution studies, no decrease in radiostrontium absorption rates was observed, even during prolonged periods of administration, or when strontium concentrations were increased (66). Calcium was substituted more readily than radiostrontium, regardless of level of dosage (66). Although high plasma levels of Sr tended to indicate increased strontium absorption, strontium excretion was a better indication of successful radioactive substitution.

Recently, Rousselet et al. (41) showed that an overdose of vitamin D in rats increased renal elimination of strontium, and brought about some removal of strontium from bone (41). Stable strontium is not considered to decrease absorption of $^{90}Sr$ in man, but it will inhibit calcium absorption. Absorption of stable and radioactive strontium is proportional to dose (66).

Solanum malacoxylon, Sendt. (S. glaucophyllum) studies

In 1974, Wasserman (45) reported that extracts from Solanum malacoxylon, Sendt. (S. glaucophyllum) reversed significantly the inhibitory effect of dietary strontium in chicks. S. malcoxylon, a South American plant of the potato-tomato family, counteracts the inhibitory action of dietary strontium, thereby suggesting that the plant contains a factor that mimics the action of $1,25\text{-}(OH)_2D_3$. This is the first such factor that has been identified from a botanical source (45).

S. malacoxylon factor is water soluble and is extracted readily from the plant by aqueous or other highly polar solvents, and could be a derivative of the $D_3$-metabolite containing a highly polar moiety (45). The plant factor stimulates the kidney 1-hydroxylase system and allows $25\text{-}OH\text{-}D_3$ hydroxylation to proceed even in the presence of strontium.

First observed in diseased Argentine cattle, "Enteque seco", is a disease characterized by extensive soft tissue calcification that follows repetitive consumption of S. malacoxylon (45). An aqueous extract of the plant caused increased absorption of calcium and phosphorus in cattle. Derived analogs from S. malacoxylon with vitamin D acted faster and faded faster than massive doses of vitamin D, and appeared to cause an increase in calcium-binding activity in

strontium rachitogenic rabbits (45).

The plant factor functions by an actinomycin D-sensitive mechanism, similar to that of vitamin D, which induces CaBP formation which then enhances calcium transport. Evidence for the mechanism was found by injection of actinomycin D which inhibited the synthesis of CaBP at the DNA transcription site of chick intestinal mucosa (67). Furthermore, aqueous extracts of Solanum failed to mobilize bone calcium in vitamin D-deficient rats fed a low calcium diet, while 1,25-$(OH)_2D_3$ was effective in that regard (68).

In studies conducted by Uribe et al. (69), the administration of an aqueous extract of the leaves from S. malacoxylon to vitamin D-deficient rats fed a normal calcium and normal phosphorus diet increased markedly serum calcium concentration within 48 hours. The extract was reported to stimulate intestinal calcium transport in the vitamin D-deficient rat, but it had no effect on mobilization of calcium from bone tissue. Also the effect was not additive to that of vitamin D; it was independent of vitamin D.

Schneider et al. (70) found that administration of S. malacoxylon extract stimulated duodenal calcium absorption in the diabetic rat (1) by restoring calcium absorption depressed by dietary strontium blockage, and (2) by increasing calcium absorption across the duodenal mucosa (70). Both extract and vitamin $D_3$ acted directly on the duodenal mucosal cells to

correct calcium absorption; this activity did not require 1α-hydroxylation. The extract was effective in inducing the synthesis of vitamin D-dependent calcium-binding proteins and enhancing calcium transport by embryonic intestine in organ culture (70).

The vitamin D-like biological activity resides in its leaves. An extract of the leaves stimulated intestinal calcium absorption in chicks under conditions in which the conversion of 25-OH-$D_3$ to 1α, 25-$(OH)_2D_3$ was prevented by high dietary strontium or nephrectomy, the removal or excision of both kidneys (71). The active principle competes effectively with 1α,25-$(OH)_2D_3$ in reconstituting intestinal chromatin receptor systems, and mediating the decrease in the steady state level of renal 25-OH-$D_3$-1α-hydroxylase in vitamin D-deficient animals (71).

Proscal et al. (71) using an intestinal receptor assay, estimated 10-60 mg of the biologically active material in one kilogram of dried S. malacoxylon leaves. Their studies indicated that the plant agent may be a structural analog of 1α,25-$(OH)_2D_3$, and that its isolation is quite feasible. Only steroids possessing the characteristic seco-steroid backbone unique to vitamin D with hydroxyls at both the 25- and the 1α position, will interact effectively with the same receptor system, and they are the only true structural analogs of the natural hormone. S. malacoxylon has 3-hydroxy-seco-steroid glycosides with approximately six

sugar residues and an estimated molecular weight of 1500 daltons (71).

Cestrum diurnum, L. studies

Wasserman et al. found evidence for 1,25-$(OH)_2D_3$-like substances in the domestic plant, Cestrum diurnum, L., day jassamine, a shrub implicated in calcinosis of grazing animals in Florida.[5] The plant displayed biological activity similar to S. malacoxylon. C. diurnum, in the diet or as an absorbed extract, reversed the inhibitory effects of high strontium diets on calcium absorption and CaBP synthesis. It showed responses shared by 1,25-$(OH)_2D_3$ and S. malacoxylon, and enhanced intestinal cyclic AMP (cAMP) levels in strontium-inhibited animals. The leaves of C. diurnum contained approximately 30,000 IU vitamin $D_3$-equivalents/kg and at least two principles like 1,25-$(OH)_2D_3$ in structure. Use of C. diurnum in the diet of strontium-inhibited animals caused excessive mineral absorption and eventual calcinosis.

Later studies by Wasserman et al. (72) showed that C. diurnum restored physiological intestinal CaBP synthesis and increased calcium absorption in the cholecalciferol-deficient chick. They estimated the levels of cholecalciferol-equivalents in

---

[5] Wasserman, R.H., Corradino, R.A., Krook, L.P. & Taylor, A.N. (1975) Evidence for 1,25-dihydroxycholecalciferol-like substance in the domestic plant, Cestrum diurnum. Fed. Am. Soc. Exp. Biol. Fed Proc. 34, 893. (Abstract)

the dried leaf at about 30,000 to 35,000 IU/kg (72). C. diurnum differed from water soluble S. malacoxylon in that it was extractable with methanol:chloroform. The extract interacted with the intestinal 1 ,25-$(OH)_2D_3$ cytosol receptor.

**Side-chain analogs**

In order to ascertain alternate structural-activity relationships of vitamin $D_3$ for medical uses, analogs and metabolite preparations have been studied. Many analogs of vitamin $D_3$ metabolites have been synthesized by several groups and tested widely in renal osteodystrophy, hypoparathyroidism, and other bone diseases as for 1,25-$(OH)_2D_3$ (33).

Johnson and Okamura chemically synthesized a homologous series of side-chain analogs of 25-OH-$D_3$, maintaining the tertiary hydroxyl moiety characteristic, in which only the length of the side-chain was modified.[6] The analogs stimulated bone calcium mobilization and showed significant activity in mediating intestinal calcium transport, especially in strontium-inhibited systems and osteolytic conditions. Although five analogs were prepared, their

---

[6]Johnson, R.L. & Okamura, W.H. (1975) Synthesis and biological activities of side-chain analogs on 25-hydroxy-cholecalciferol (25-hydroxy-vitamin $D_3$). (SPON: Weimberg, R.). Fed. Am. Soc. Exp. Biol., Fed. Proc. 34, 893. (Abstract).

bioassays showed trinor, dinor and nor analogs had only one-half the activity of 25-OH-$D_3$.

Mahgoub found that the biological activity of hydroxy-vitamin $D_3$ derivatives in rat fetal bone cultures increased intestinal calcium absorption and vitamin $D_3$ binding activity.[7] Of all the analogs tested, 1,25-$(OH)_2D_3$ had the greatest effect on calcium mobility, 1$\alpha$-OH-$D_3$ was next efficient, and 24,25-$(OH)_2D_3$ the least. That order of activity was paralled by their competitive binding and intestinal calcium transport ability.

Osborn and Norman developed steroid analogs of 25-OH-$D_3$ for use as competitors in determining the specificity of serum binding proteins.[8] Among the compound complexes formed, the results indicated that analog 25-OH-$D_3$ had the highest affinity for binding proteins.

Deluca (33) reported that 1$\alpha$-OH-$D_3$, an analog of 1,25-$(OH)_2D_3$ had biological activity equal to 1,25-$(OH)_2D_3$ in chicks, and 20-50% activity in rats. This biological activity occurs from single hydroxylation in the liver and to some extent in the intestine without binding to the cytosol

---

[7]Mahgoub, A. (1975) The biological activity of hydroxy (OH) vitamin $D_3$ derivatives in rat fetal bone cultures, in vitro. (SPON: Miller, O.N.). Fed. Am. Soc. Exp. Biol., Fed. Proc. 34, 893. (Abstract).

[8]Osborn, T.W. & Norman, A.W. (1975) Measurement of 25-hydroxycholecalciferol by a specific chick plasma competitive binding assay. Fed. Am. Soc. Exp. Biol., Fed. Proc. 34, 893. (Abstract).

receptor. But, its activity does not resemble that of $1,25\text{-}(OH)_2D_3$ in vitro in the mobilization of bone calcium.

At the present time analogs are difficult to prepare. Extracts are less costly alternatives, and may prove to be more effective than analogs in increasing calcium intestinal transport and deposition in bone, when strontium-inhibition is acute.

## SUMMARY

Strontium in stable or radioactive form is not an essential or desirable trace element in human beings or animals. The population is exposed to strontium through air, water, soil and food. High concentrations of strontium are found most frequently in calcium-rich foods, such as milk and green vegetables. Strontium is most sensitive to detection by neutron activation analysis and, secondly, by x-ray fluorescence.

During steady state, adult man absorbs 20-40% of ingested strontium and 40-80% of ingested calcium from a uniform diet. Chemically, calcium and strontium are similar, and in the body they compete for absorption and deposition in bone. Absorbed strontium inhibits 1α-hydroxylation of 25-hydroxycholecalciferol, synthesis of calcium-binding protein and absorption of calcium in man and animals. Strontium absorption is affected most by the levels of calcium and phosphorus in the diet and the demands for calcium by the body. If dietary calcium is adequate, the body absorbs calcium preferentially, and excretes strontium in the urine. Strontium discrimination occurs in the gastrointestinal lining, kidney, mammary glands, placenta and bone tissues. Preferential discrimination against strontium occurs before birth and during infancy, childhood and adulthood. Strontium absorption is greater in infants than adults. Breast-fed infants tend to be in positive calcium balance and negative

strontium balance, whereas bottle-fed infants are in positive strontium balance.

Absorbed radionuclides of strontium are most hazardous because of their bone-seeking tendencies and continued beta particle emission after deposition. Absorption of radiostrontium predisposes human beings to two forms of carcinoma, leukemia and osteosarcoma.

Methods for control of strontium absorption and prevention of its retention in the body are under continual investigation. Presently, the use of vitamin D analogs and extracts of some plants, Solanum malacoxylon, Sendt. and Cestrum diurnum L. show promise as agents to reverse the inhibitory effects of high strontium diets on synthesis of vitamin D metabolites and calcium-binding protein for calcium absorption in the body.

# LITERATURE CITED


1. Dorland's Illustrated Medical Dictionary. (1974) 25th Edition. (Friel, J.P., ed.), 1748 pp. W.B. Saunders, Philadelphia.

2. Goodenough, R.D. & Stenger, V.A. (1973) Magnesium, calcium, strontium, barium, and radium. In: Comprehensive Inorganic Chemistry (Bailar, J.C., Emeleus, H.J., Nyholm, R. & Trotman-Dickenson, A.F., eds.), pp. 591-664, Pergamon Press, Great Britain.

3. Sneed, M. & Maynard, J.L. (1942) Strontium nitrate. In: General Inorganic Chemistry (8th Edition), pp. 860-862, D. Van Nostrand Co., Inc., New York.

4. CRC Handbook of Chemistry & Physics, CRC Press, Cleveland, Ohio. The Elements, 54th Edition. (1973-1974), B-31.

5. Comar, C.L. & Wasserman, R.H. (1964) Strontium. In: Mineral Metabolism, an Advanced Treatise, Volume II-The Elements-Part A (Comar, C.L. & Bronner, F., eds.), pp. 523-572, Academic Press, New York.

6. Sunderman, D.N. & Townley, C.W. (1960) The Radiochemistry of Barium, Calcium, and Strontium. National Academy of Sciences-National Research Council-Nuclear Science Series. 117 pp. U.S. Atomic Energy Commission, Battelle Memorial Institute, Columbus, Ohio.

7. Wood, H.J., Keenan, C.W. & Bull, W.E. (1968) Inorganic chemistry; the alkali and alkaline earth elements. In: Fundamentals of College Chemistry, 2nd Edition, pp. 293-307, Harper & Row, Publishers, New York.

8. Faure, G. & Powell, J.L. (1972) Strontium Isotope Geology, 278 pp. Springer-Verlag, New York.

9. Mitchell, R.L. (1957) Trace element content of plants. Research: Sci. & its Application in Industry 10, 357-359.

10. Johnson, H. (1955) The strontium deposits of Port Au Port Peninsula. In: Contributions to the Economic Geology of Western Newfoundland. Geological Survey of Canada-Bulletin 27, 1-19.

11. Bohinski, R.C. (1976) Methods of biochemistry. In: Modern Concepts in Biochemistry, 2nd Edition (Bush, D.H. & Shull, H., eds.), pp. 4-92, Allyn and Bacon, Inc., Boston.

12. Christian, G.D. (1971) Atomic spectroscopic methods. In: Analytical Chemistry (Atkinson, G., ed.), pp. 358-372, Xerox College Publishing, Waltham, Massachusetts.

13. Hercules, D.M. (1971) Radiochemical methods of analysis. In: Analytical Chemistry (Atkinson, G., ed.), pp. 400-416, Xerox College Publishing, Waltham, Massachusetts.

14. Moeller, T. (1952) Atomic nuclei and properties related thereto. In: Inorganic Chemistry, an Advanced Textbook, pp. 16-78, John Wiley & Sons, Inc., New York.

15. Jury, R.V., Webb, M.S.W. & Webb, R.J. (1960) The spectrochemical determinations of total Sr in bone, milk, and vegetation. Anal. Chim. Acta. 22, 145-152.

16. Hamada, G.H. & Kruger, P. (1965) Methods of assessing fallout. In: Radioactive Fallout, Soils, Plants, Foods, Man (Fowler, E.B., ed.), pp. 287-301, Elsevier Publishing Company, Amsterdam.

17. Methods of Radiochemical Analysis. (1959) Report of a Joint WHO/FAO Expert Committee. U.N. Food and Agriculture Organization-FAO Atomic Energy Series. No. 1. 116 pp., World Health Organization, Rome.

18. Arnold, J.R. & Martell, E.A. (1959) The circulation of radioactive isotopes. In: Chemistry in the Environment, Reading from Scientific American, pp. 272-281, W.H. Freeman and Company, San Francisco.

19. Garner, R.J. (1972) Transfer of Radioactive Materials from the Terrestrial Environment to Animals and Man, 57 pp., CRC Press, Cleveland, Ohio.

20. Russell, R.S. (1966) Behavior of radioactive material in soil. In: Radioactivity and Human Diet (Russell, R.S., ed.), pp. 107-125, Pergamon Press, Oxford.

21. Russell, R.S. (1966) Entry of radioactive materials into plants. In: Radioactivity and Human Diet (Russell, R.S., ed.), pp. 89-104, Pergamon Press, Oxford.

22. Bruce, R.S., Bartlett, B.O. & Russell, R.S. (1967) Time course of the transfer of strontium-90 through food chains to man. In: Strontium Metabolism (Lenihan, J.M.A., Loutit, J.F. & Martin, J.H., eds.), pp. 33-39, Academic Press, New York.

23. Roushdy, H.M., Abdel Salam, M.A., Moloukhia, M.K. & Batief, Sawsan Abdel. (1974) Availability of strontium-90 to various Egyptian plants through environmental contamination (IAEA-SM-175/44). In: Comparative Studies of Food and Environmental Contamination (FAO, IAEA, WHO, eds.), pp. 259-270, International Atomic Energy Agency, Vienna.

24. Comar, C.L. (1966) Radioactive materials in animals-entry and metabolism. In: Radioactivity and Human Diet (Russell, R.S., ed.), pp. 129-157, Pergamon Press, Oxford.

25. Radioactive Materials in Food and Agriculture. (1960) Report of an FAO Expert Committee. U.N. Food and Agriculture Organization-FAO Atomic Energy Series, No. 2. 123 pp. Food and Agriculture Organization of the United Nations, Rome.

26. Agricultural and Public Health Aspects of Radioactive Contamination in Normal and Emergency Situations. (1964) Papers presented at the seminar, Achevenignen, The Netherlands, and sponsored jointly by FAO, WHO, and IAEA. U.N. Food and Agriculture Organization-FAO Atomic Energy Series, No. 5. 421 pp. Food and Agriculture Organization of the United Nations, Rome.

27. Radionuclides in Foods. 97 pp. Committee on Food Protection, Food and Nutrition Board. (1973) National Academy of Sciences, Washington, D.C.

28. Dietary Levels of Strontium-90 and Cesium-137. (1962) A summary of world information. U.N. Food and Agriculture Organization-FAO Atomic Energy Series. No. 3. 78 pp. Food and Agriculture Organization of the United Nations, Rome.

29. Peige, Y., Eisenberg, A., Proulov, Y. & Klopfer, J. (1974) Long-lived radionuclides in food: strontium-90 and cesium-137 in the Israel diet (IAEA-SM-175/49). In: Comparative Studies of Food and Environmental Contamination (FAO, WHO, IAEA, eds.), pp. 26-35, International Atomic Energy Agency, Vienna.

30. Comar, C.L. (1967) Some principles of strontium metabolism: implications, applications, limitations. In: Strontium Metabolism (Lenihan, J.M.A., Loutit, J.F. & Martin, J.H., eds.), pp. 17-33, Academic Press, New York.

31. Irving, J.T. (1973) Calcium and Phosphorus Metabolism, pp. 20-85, Academic Press, New York.

32. Taylor, A.N. & Wasserman, R.H. (1965) A vitamin $D_3$-dependent factor influencing calcium binding by homogenates of chick intestinal mucosa. Nature, London 205, 248-250.

33. DeLuca, H.F. (1976) Metabolism of vitamin D: current status. Am. J. Clin. Nutr. 29, 1258-1270.

34. Mitchell, H.S., Rynbergen, H.J., Anderson, L. & Dibble, M.V. (1976) Nutrition in Health and Disease, pp. 82-85, J.B. Lippincott Co., Philadelphia.

35. DeLuca, H.F. (1973) New forms of vitamin $D_3$ and their potential applications. Nutr. News 36, 13-16.

36. Wasserman, R.H., Corradino, R.A. & Taylor, A.N. (1968) Vitamin D dependent calcium-binding protein. J. of Biol. Chem. 243, 3978-3986.

37. Comar, C.L., Wasserman, R.H., Ullberg, S. & Andrews, G.A. (1957) Strontium metabolism and strontium-calcium discrimination in man. Proc. Soc. Exp. Biol. and Med. 95, 386-390.

38. Omdahl, J.L. & DeLuca, H.F. (1971) Strontium induced rickets: metabolic basis. Science 174, 949-951.

39. Omdahl, J.L. & DeLuca, H.F. (1972) Rachitogenic activity of dietary strontium, inhibition of intestinal calcium absorption and 1,25-dihydroxycholecalciferol synthesis. J. of Biol. Chem. 247, 5529-5536.

40. Corradino, R.A., Ebel, J.G., Craig, P.H., Taylor, A.N. & Wasserman, R.H. (1971) Calcium absorption and the vitamin $D_3$-dependent calcium-binding protein, inhibition by dietary strontium. Calc. Tiss. Res. 7, 81-92.

41. Rousselet, F., El Solh, N., Maurat, J.P., Gruson, M. & Girard, M.L. (1975) Strontium et metablisme calcique. Interaction strontium-vitamine D. C.R.Soc. Bio. (paris) 169, 322-339.

42. Fabrikant, J.I. (1972) Radiobiology, 421 pp., Year Book Medical Publishers, Inc., Chicago.

43. Wasserman, R.H., Lengemann, F.W., Thompson, J.C.Jr. & Comar, C.L. (1965) The transfer of fall-out radionuclides from diet to man. In: Radioactive Fallout, Soils, Plants, Foods, Man (Fowler, E.B., ed.), pp. 204-244, Elsevier Publishing Co., Amsterdam.

44. Wasserman, R.H. (1963) Vitamin D and the absorption of calcium and strontium in Vivo. In: The Transfer of Calcium and Strontium Across Biological Membranes (Wasserman, R.H., ed.), pp. 211-228, Academic Press, New York.

45. Wasserman, R.H. (1974) Calcium absorption and calcium-binding protein synthesis: Solanum malacoxylon reverses strontium inhibition. Science USA 183, 1092-1094.

46. Carr, R.E.F. (1967) An attempt to quantitate the short-term movement of strontium in the human adult. In: Strontium Metabolism (Lenihan, J.M.A., Loutit, J.F. & Martin, J.H., eds.), pp. 139-146, Academic Press, New York.

47. Tipton, I.H. & Cook, M.J. (1963) Trace elements in human tissue, Part II. Adult subjects from the United States. Health Physics 9, 103-105.

48. Hodges, R.M., Mcdonald, N.S., Nusbaum, R.E., Stearns, R., Ezimirlian, F., Splain, P. & Macarthur, S. (1950) The strontium content of human bones. J. Biol. Chem. 185, 519-524.

49. Gedalia, I., Yariv, S., Nayot, H. & Eidelman, E. (1974) The strontium concentration in developing mandibles and teeth and in enamel of non-erupted and erupted-teeth of human beings. In: Trace Element Metabolism in Animals-2 (Hoekstra, W.G., Suttie, J.W., Ganther, H.E. & Mertz, W., eds.), pp. 461-464, University Park Press, Baltimore.

50. Kuhnlein, H.V. & Calloway, D.H. (1976) Trace elements in preindustrial and contemporary native American teeth. J. of Nutr. 106, 21.

51. Widdowson, E.M., Slater, J.E., Harrison, G.E. & Sutton, A. (1960) Absorption, excretion, and retention of strontium by breast-fed and bottle-fed babies. Lancet 2, 941-944.

52 Christensen, G.C., Alstad, J., Kvale, E. & Pappas, A.C. (1975) Strontium-90 in human bone in Norway 1956-1972. Health Physics 28, 677-684.

53. Muller, J. & Thomas, J. (1969) Strontium retention in man. In: Delayed Effects of Bone-seeking Radionuclides (Dougherty, J.H. & Taylor, G.N., eds.), pp. 51-60, University of Utah Press, Salt Lake City, Utah.

54. Wasserman, R.H., Comar, C.L., Nold, M.M. & Lenegemann, F.W. (1957) Placental transfer of calcium and strontium in the rat and rabbit. Am. J. Physiol. 189, 91-97.

55. Widdowson, E.M., McCance, R.A., Harrison, G.E. & Sutton, A. (1963) Effect of giving phosphate supplements to breast-fed babies on absorption and excretion of calcium, strontium, magnesium and phosphorus. Lancet 2, 1250-1251.

56. Comar, C.L. (1966) Transfer of strontium-90 into animal produce. In: Radioactivity and Human Diet (Russell, R.S., ed.), pp. 247-273, Pergamon Press, Oxford.

57. Bartley, J.C. & Reber, E.F. (1961) Toxic effects of stable strontium in young pig. J. of Nutr. 75. 21-28.

58. Warren, J.M. & Spencer, H. (1976) Metabolic balances strontium in man. In: Clinical Orthopaedics and Related Research (Urist, M.R., ed.), pp. 307-319, J.B. Lippincott Co., Philadelphia.

59. Kidman, B., Tutt, M.L. & Vaughan, J.M. (1950) The retention and excretion of radioactive strontium and yttrium ($^{89}Sr$, $^{90}Sr$, $^{90}Y$) in the healthy rabbit. J. Path. and Bact. 62, 209-212.

60. Thorne, M.C. & Vennart, J. (1976) The toxicity of $^{90}Sr$, $^{226}Ra$, and $^{239}Pu$. Nature 263, 555-558.

61. Borovik, S.A. & Kalinin, S.K. (1958) Trace elements in milk: a review. In: Dairy Sci. Abstr. (Archibald, J.G., ed.), 20, 712-720.

62. Lough, S.A., Hamada, G.H. & Comar, C.L. (1960) Secretion of dietary strontium-90 and calcium in human milk. Proc. Soc. Exp. Biol. and Med. 104, 194-198.

63. Stevenson, A.F.G. (1975) The influence of age and sex on the activity ratio of yttrium-90 to strontium-90 in the rat skeleton after incorporation of strontium-90. Health Physics 29, 285-290.

64. Nordio, S, Donath, A., Macagno, F. & Gatti, R. (1971) Chronic hypomagnesemia with magnesium-dependent hypocalcemia: a study of the relationship between magnesium, calcium, and strontium. Acta. Pade. Scandinavica 60, 441-455.

65. Escanero, J., Carre, M. & Miravet, L. (1976) Effects des differents metabolites de la vitamine $D_3$ et de la concentration calcique sur l'absorption intestinale du strontium. C. R. Soc. Bio. (Paris) 170, 47-53.

66. Spencer, H., Lewin, I. & Samachson, J. (1967) Influence of dietary and hormonal factors on radiostrontium metabolism in man. In: Strontium Metabolism (Lenihan, J.M.A., Loutit, J.F. & Martin, J.F., eds), pp. 111-129, Academic Press, New York.

67. Corradino, R.A. & Wasserman, R.H. (1970) Strontium inhibition of vitamin $D_3$-induced calcium-binding protein (CaBP) and calcium absorption in chick intestine. Proc. Soc. Exp. Biol. and Med. 133. 960-963.

68. Corradino, R.A. & Wasserman, R.H. (1974) 1,25-dihydroxycholecalciferol-like activity of Solanum malacoxylon extract on calcium transport. Nature 252, 716-71

69. Uribe, A., Holick, M.F., Jorgensen, N.A. & DeLuca, H.F. (1974) Action of Solanum malacoxylon on calcium metabolis in the rat. Biochemical and Biophysical Research Communications 58, 257-262.

70. Schneider, L.E., Wasserman, R.H. & Schedl, H. (1975) Depressed duodenal calcium absorption in the diabetic rat: restoration by Solanum malacoxylon. Endocrinology 97, 649-653.

71. Procsal, D.A., Henry, H.L., Hendrickson, H. & Norman, A.W. (1976) 1$\alpha$,25-Dihydroxyvitamin $D_3$-like component present in the plant Solanum glaucophyllum. Endocrinology 99, 437-444.

72. Wasserman, R.H., Corradion, R.A., Krook, L.P., Hughes, M.R. & Haussler, M.R. (1976) Studies on the 1$\alpha$,25-dihydroxycholecalciferol-like activity in a calcinogenic plant, Cestrum diurnum, in the chick. J. of Nutr. 106, 457-465.

# STRONTIUM - BIOCHEMICAL INTERACTIONS AND INHIBITIONS IN ANIMALS AND MAN

by

CHERYL ANN CATOR SMYERS

A.A.S., Morrisville Agricultural and Technical College
State University of New York, 1972

B.S., Rochester Institute of Technology, 1974

---

AN ABSTRACT OF A MASTER'S REPORT

submitted in partial fulfillment of the
requirements for the degree
MASTER OF SCIENCE

Department of Foods and Nutrition
Kansas State University
Manhattan, Kansas

1977

## ABSTRACT

Strontium in stable or radioactive form is not an essential or desirable trace element in human beings or animals. The population is exposed to strontium through air, water, soil and food. High concentrations of strontium are found most frequently in calcium-rich foods. Adult man absorbs 20-40% of ingested strontium and 40-80% of ingested calcium from a uniform diet. Chemically, calcium and strontium are similar, and in the body they compete for absorption and deposition in bone. Absorbed strontium inhibits 1$\alpha$-hydroxylation of 25 hydroxy-cholecalciferol synthesis of calcium-binding protein and absorption of calcium in man and animals. Strontium absorption is affected most by the levels of calcium and phosphorus in the diet and the demands for calcium by the body. Preferential discrimination against strontium occurs in the gastrointestinal lining, kidney, mammary glands, placenta and bone tissues during all ages. Absorbed radionuclides of strontium are most hazardous because of their bone-seeking tendencies and continued beta particle emission after deposition. Retained radiostrontium predisposes human beings to two forms of carcinoma. Methods for control of strontium absorption and prevention of its retention in the body are under continual investigation. Presently, the use of vitamin D analogs and extracts of some plants, Solanum malacoxylon, Sendt. and Cestrum diurnum L. show promise as agents to reverse the inhibitory effects of high strontium diets on synthesis of vitamin D metabolites and calcium-binding proteins.