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Introduction

Metabolism of radioactive isotopes produced in the process of nuclear fission has been a field of interdisciplinary research for over four decades and biomedical implications of internal contamination with organotropic radionuclides continues generating considerable data, concerning mechanisms and therapeutic management of internally deposited radioisotopes.

In a nuclear explosion over 400 radioactive isotopes are released in the biosphere (1). Among those, about 40 radionuclides are of a potential hazard for man. Of particular interest to the field of medicine are those isotopes whose organospecificity and long half life present a danger of irreversible tissue damage or induction of malignant alterations. Both early or delayed fallout result in deposition of radioactive material in the human external environment with a potential entry into the human body by oral or parenteral route (wounds, inhalation), and continuous radiation exposure of the internal organs and tissues to the radiation produced by the incorporated radioisotopes, can lead to various pathological entities, including malignant neoplasms. Incorporated radionuclides are partly diminished in the processes of radioactive decay and biological elimination, which are of no consequence in reducing radiation damage with those isotopes whose long half-life and firm tissue incorporation necessitates application of therapeutic removal from the contaminated organism. Radiation effects of internally deposited radionuclides depend on their chemical nature, solubility, half-life, type of radioactive decay, the tissue of the radionuclide incorporation and physiological factors determining their metabolic fate. High organospecificity of certain fission products will result in a radiation damage to the selective tissues, whereas some other radionuclides which are uniformly distributed in the body fluids will result in a relatively uniform exposure of the various organs to their radiation. Some radionuclides produce detectable tissue damage soon after their incorporation to the tissues of high radiosensitivity whereas the other radioisotopes may result in the induced somatic and genetic changes as their late effects. From the biomedical point of view an approach to the problem of internal contamination should primarily consider radionuclide organospecificity rather than their physical or chemical characteristics, because various radioisotopes of the same element have entirely different organs of ultimate incorporation. The fate of

radioisotopes, however will depend on the various factors, including their chemical and physical nature, solubility, particle size, homeostasis, type of decay, biological decorporation and elimination from the contaminated organism. Some of the fission products will behave like their stable homologues in a normal organism and will be handled by the same mechanisms of homeostasis, whereas the other radionuclides will be totally foreign to the structural elements of the normal organism and their incorporation and elimination from the body will be the subject of the other elimination processes which are frequently non-homeostatic. Radioisotopes which have no specific target organs will be rapidly eliminated from the organism by the processes of natural elimination. This however, is not a rule as some highly organospecific radioisotopes (e.g. iodine) will be concentrated in their natural target organ -- thyroid, whereas other radionuclides which are not normally present in nature (e.g. plutonium) will also demonstrate high organospecificity, with osteotropic characteristics due to their metabolic pathways similar to the normal constituents of the calcified tissue. Incorporation of such radioisotopes in their target organs can result in considerable tissue damage, as some of those isotopes have extremely long half-lifes and decay by the corpuscular (alpha and beta) radiation resulting in high probability of malignant alteration in their, frequently highly radiosensitive, target organs.

Nuclear fission produced radioisotopes are distributed in the organism by bloodstream after entering the internal environment by ingestion, inhalation, or through contaminated wounds. The extent of their entry in the internal environment depends on their physical properties and solubility in the body fluids. The ultimate site of tissue deposition will be determined by their chemical properties. Various radioisotopes have different portals of entry into the organism, some are preferentially absorbed in gastrointestinal mucosa, others gain an access to the bloodstream via respiratory tract, whereas the others preferentially enter the body fluids through the wounds or by direct intravascular administration. The length of the radioisotope retention in the body is determined by its physical, biological and effective half-life, mechanisms of entry, quantity, target organ, and the processes of elimination. Some fission products are preferentially absorbed in the intestine (calcium, strontium, iodine, cesium, etc.), whereas the others are hardly absorbed by ingestion (actinides) and are primarily incorporated by the inhalation or through contaminated wounds. Most of the fission products are rapidly eliminated from the body after initial nuclear weapon produced fallout and main biomedical hazard is due to the radioisotopes of high organospecificity and long half-life,

such as cesium-137, strontium-90, yttrium-90, carbon-14, tritium, iodine-131, and transuranic elements, which invariably produce pathologic changes, including malignant tumors as well as spontaneous and induced mutations as their genetic effects in the contaminated organism.

Routes of Entry and Distribution

There are four main routes of internal contamination (1) ingestion and gastrointestinal absorption, (2) inhalation and trans-alveolar transfer to the blood stream, (3) percutaneous absorption, and (4) entry to the internal environment through the wounds or by direct injection into the blood stream.

Ingestion

Gastrointestinal absorption of the nuclear fission products is different for the various radionuclides. Some of the ingested radioactive isotopes preferentially enter the blood stream via intestinal muscosa, whereas some other isotopes are not absorbed in any significant amount. Of those isotopes whose principal route of entry is gastrointestinal absorption, most significant ones are the isotopes of cesium (Cs-137), strontium (Sr-90), cobalt (Co-60), iodine (I-131), phosphorus (P-32), mercury (Hg-197, Hg-203), radium (Ra-226), and tritium (H-3). Gastrointestinal absorption is an important route of entry of the osteotropic alkaline earth isotopes such as strontium-90. Gastrointestinal absorption is particularly important as a consequence of the delayed fallout hazards because of the contaminated biosphere and the food contaminated by the nuclear fission products (farm produce, milk products). Homeostatic mechanisms that govern the transfer of radioactive isotopes across the intestinal mucosa, however, can discriminate against some of the radioisotopes which are foreign to the organism, favoring absorption of their homologues which are involved in the normal homeostasis. Over 90% of the entire process of discrimination of strontium takes place in the gastrointestinal tract, where calcium is preferentially absorbed and this phenomenon constitutes one of the methods of therapeutic removal of radioactive strontium via intestinal tract. Other sites where discrimination processes against radioactive strontium occur include renal tubules, mammary gland and placenta where calcium reabsorption is favored. These biological membranes represent the sites of the homeostatic protection against potentially hazardous radionuclides. Mechanism

of preferential absorption of calcium in relation to strontium in the intestinal mucosa was partly addressed by the processes of diffusion and active transport for calcium, whereas the transfer of strontium from the intestinal lumen to circulation is mainly via diffusion (2). Ingestion of cesium (Cs-137) results in rapid and high rate of entry into the bloodstream. There are numerous reported cases of accidental contamination with Cs-137 in humans (3, 4). Gastrointestinal absorption of radioactive cobalt (Co-60) is facilitated by the presence of stable cobalt, which is an important factor in consideration of therapeutic management of internal contamination with Co-60 entering the circulation via gastrointestinal route. The percent of the whole body retention of cobalt is similar for intravenous administration and ingestion, with about 20% of Co-60 retained in the liver after either oral or intravenous contamination. Intestinal absorption of radioactive iodine (I-131) is an important route of accidental contamination because of its transfer from the contaminated biosphere to the human body via food chain (pasture - dairy products - man). There are numerous reports in the literature on the protective measures against accidental ingestion of radioactive iodine, (including disposal of contaminated cattle feed, milk, and dairy products (5, 6). In all cases of accidental ingestion of radioactive iodine, thyroid bioassay and immediate institution of therapeutic management should be applied to the contaminated patients and periodical monitoring for the evidence of hypothyroidism should be maintained for several years in each case (7). Accidental contamination with mercury (Hg-197, Hg-203) has been reported and early gastric lavage has produced significantly reduced body burden. Oral contamination with radioactive phosphorus (P-32) should be handled in the same manner as the treatment for non-radioactive phosphorus poisoning (potassium permanganate gastric lavage). Accidental contamination with P-32 via intestinal mucosa has not been reported as a serious hazard from the nuclear fission fallout.

Intestinal absorption of radium (Ra-226) is an important route of inducing skeletal malignancies. Over 30 percent of Ra-226 is absorbed in the intestine after accidental ingestion, and is almost entirely deposited in the skeleton (8 - 10). Ingestion of Radium (Ra-226) has been reported in the classic work on internal contamination in the dial painters ingesting luminous paints containing Ra-226 (11, 12). Various pathological consequences followed Ra-226 ingestion, including osteogenic sarcoma, fibrosarcoma, paranasal and mastoid carcinoma, aplastic anemia and leukemia (13, 14).

Other radionuclides that enter the circulation via gastrointestinal tract include tritium (H-3) which penetrates intestinal mucosa in the form of tritiated water (15), and uranium isotopes (U-234, U-235, U-238) which present a high biomedical hazard because of their long half-lifes, nephrotoxicity (U-238) and retention in the skeletal tissue (U-234, U-235), with a high potential of inducing malignant changes in the bone and hematopoietic tissues.

Inhalation

Kinetics of the bronchoalveolar deposition and transalveolar passage of radionuclides into the blood-stream is an extremely complex area both from the viewpoint of physiology and radiation toxicology (16). Inhaled radioactive particles are deposited in the upper bronchial tree, on the alveolar surfaces or, if soluble they are absorbed into the systemic circulation. Classic reports on the quantitative data concerning deposition of the radioactive particles in bronchoalveolar tree have been reported over 35 years ago (17, 18) and since that time, a considerable number of reports have been published concerning the pathways of the various radioisotopes in the respiratory system. For the evaluation of the radiation hazard of inhaled radioactive particles, a general model of their metabolic behavior in the respiratory system was adopted by the ICRP, in 1955 (19) and was subsequently revised (20),with the emphasis on the significance of different variables determining metabolic fate of inhaled radioactive particles. According to that model, about 75% of inhaled radioactive particles are deposited in the respiratory tree and 25% are immediately exhaled. About 50% of the inhaled particles are deposited in the upper bronchial tree with subsequent ascending movement by the cilliary epithelium to the nasopharynx from which site they are swallowed and handled by the mechanisms of their gastrointestinal kinetics. This is an important factor in contamination with actinides, whose intestinal absorption is negligible whereas their pulmonary deposition represents a major radiotoxicologic hazard and translocation from the respiratory to the gastrointestinal system is one one of the aims of therapeutic management of accidental contamination with inhaled actinides. About 25% of inhaled particles are deposited on the alveolar surfaces and their metabolic behavior at this site largely depends on their solubility. In general about 10% of particles reaching alveolar surfaces are transferred into the systemic circulation and remaining 15% ascends up the bronchial tree and is ultimatly eliminated by either expectoration or by translocation to the gastrointestinal tract.

Inhalation of radioactive particles is the main internal exposure route in contamination with actinides, (Americium, Plutonium, Uranium, Curium, Polonium, Radium, Thorium), Cobalt, Cerium, Iodine, Tritium. There are quantatitive differences in the kinetics of different radioisotopes gaining access to the body via respiratory tract, but the ultimate distribution after they reach systemic circulation will depend on their metabolic pathways and organospecificity. There are differences in distribution as a consequence of the portal of entry, solubility, particle size, and chemical form of the radionuclide. Americium transport to extrapulmonary tissues after inhalation will be greater if the isotope is in a citrate form, with consecutive lesser body burden and target organ (liver, bone) accumulation if the radionuclide is present in the form of a nitrate. If Am-241 is inhaled as an oxide, the target organs will be tracheobronchial lymph nodes, liver, lung, bone, and thyroid, in descending order. In accidental contamination with undetermined chemical form of Am-241 in humans, by inhalation, main target organs were bone and the liver (21). Americium is eliminated from the lung tissue by its absorption in the blood and elimination by endobronchial ciliary mechanisms and expectoration or ingestion after reaching nasopharynx (22). Am-241 that gains access into the systemic circulation from the lung is equally distributed in bone (45%) and liver (45%) for all of its compounds.

Californium (Cf-252) is another actinide causing accidental internal exposure by inhalation. After gaining access to perialveolar circulation, it is ultimately deposited in bone. There are few reported cases of human contamination with Cf-252 by inhalation with described rapid deposition in the bone tissue (23).

Cerium (Ce-141, Ce-144) contamination via respiratory tract results in its deposition in the lung, liver, and bone. There is a difference in organospecificity between long and short lived cerium isotopes. Cerium (Ce-144) with longest physical half-life (284 days) is preferentially deposited in the skeleton, whereas its short lived isotopes are preferentially deposited in the liver. Systemic absorption of cerium from the lung is less than 10 percent (24).

Cesium (Cs-137) is also a potential hazard in accidental exposure by inhalation. After entering systemic circulation from the respiratory system Cs-137 is uniformly distributed throughout the body and rapidly eliminated by the renal system.

Cobalt (Co-60) is an inhalation hazard deposited in the lung in the form of particles. The initial elimination of inhaled cobalt isotopes is rapid, with over 80 percent eliminated within the first 24 hours with remaining 20 percent removed more slowly, depending on their chemical form and particle size (25).

Curium (Cm-242, Cm-244) like the other actinides is an important internal contamination hazard in inhalation exposure. Its absorption from the lung into the systemic circulation is rapid with 15-45 percent entering perialveolar circulation and about 10 percent being deposited in the bone. There are reported cases of human inhalation exposure to Cm-244 in the form of airborne particles which permitted analysis of detection, kinetic studies, and therapeutic removal of Cm-244 (26).

Internal contamination with plutonium (Pu-239) via respiratory route of exposure is the most important way of accidental contamination and accounts for over 75% of all industrial exposures to plutonium (27). The absorption from the respiratory tract depends on the compound solubility. Soluble compounds (nitrate, citrate, fluoride are absorbed into the systemic circulation and deposited in the liver and bone within a few weeks. Insoluble plutonium compounds (oxides) retention in the lung is much longer with slow translocation into the pulmonary and tracheobronchial lymph nodes, followed by the liver uptake many years after inhalation exposure (28).

Inhalation of Polonium (Po-210) has been reported in accidental contamination in humans. This radionuclide is the least radioactive member of uranium series and results in the deposition in the skeleton (78 percent of absorbed dose) followed by the retention in the lung, liver, muscle, kidney, lymph nodes, and spleen (29, 30).

Internal contamination with radium (Ra-226) is mainly due to ingestion and contaminated wounds, with respiratory route being less important way of exposure. However, over 65 percent of radon-222 (which is formed in the body as a result of Ra-226 decay) is exhaled and Rn-222 concentration in the exhaled air is used for the estimation of quantity of Ra-226 in the body by radon breath analysis method (9). Once absorbed from the portal of entry, Ra-226 is almost entirely deposited in the skeleton (31).

Uranium isotopes constitute a considerable accidental exposure hazard after inhalation. The absorption and retention of uranium isotopes depend on their chemical form and particle size. Biological half-life in the lung is estimated to be 120 days with considerably longer half-life (1470 days) in the case of the inhalation of uranium oxides. Soluble uranium compounds are primarily absorbed by the respiratory route, with reported fatal cases of accidental inhalation in humans, causing nephrotoxic changes, including glomerular and tubular damage, azotemia, albuminuria, and tubular necrosis. These changes may be reversible with reported tolerance after subsequent exposure to soluble uranium compounds. Renal damage is caused by the chemical, rather than radiation damage to the kidney. Less soluble uranium compounds are less avidly absorbed in the lung.

Accidental internal contamination with the isotopes of iodine occurs mostly by I-131, although about ten radioactive isotopes of iodine are produced in nuclear fission. Inhalation exposure, although not a major route of iodine entry into the organism, constitutes a significant radiation hazard because of its volatility. Inhaled iodine reaches equilibrium with body fluids in less than one hour and selectively accumulates in the thyroid gland. Thyroid bioassay should be performed in each case of suspected internal contamination with I-131, and follow up studies should be performed for many years, as some patients have developed hypothyroidism as late as 17 years after exposure (7).

Tritium (H-3) presents a radiation hazard when inhaled but the radiation toxicology consequences by this route of entry are less significant than in ingestion of elemental tritium as tritiated water.

Although the internal contamination with medically significant radioisotopes via inhalation has been described in humans in nuclear weapons and industry accidental exposures there is still a need of analyzing various parameters of metabolic behavior and consequences of internal contamination with various radionuclides via respiratory route of exposure. Compartmental analysis, kinetics and autopsy data have not yet been sufficiently well defined in human exposure and further insight into the metabolic fate of inhaled radioisotopes is being derived from the animal experiments, as well as from the excretion data in humans following pulmonary exposure.

Percutaneous Absorption

Normal skin present an effective mechanical barrier to the internal contamination with most of the radionuclides. This route of entry, although least important in the transfer of the radioisotopes from the contaminated biosphere to the internal environment of the human body represents a potential concern from the standpoint of internal contamination. The studies on percutaneous absorption of transuranic elements have been described in laboratory animals with the absorption of plutonium of 2 percent through the intact skin (34). Transcutaneous absorption in these exposure studies was facilitated by the high acidity and complexing plutonium with tributylphosphate. The entry of the absorbed radionuclides was also dependent on the applied quantity of the radionuclides and the anatomic site of the skin to which the radioactivity was applied. The main pathway of the radioisotopes from the skin to the systemic circulation is through the hair follicles. The hair bulbs below their keratogenous zone are supplied by a highly vascularized connective tissue which represent a part of a normal hair papilla. This rich network of blood vessels is the principal site of transcutaneous migration of the radioisotopes from the contaminated skin into the systemic circulation. The surface epithelium (epidermis) with its primary function to protect the internal environment of the body is less important as a route of entry of the radioisotopes into the body, mainly because of its thick multilayer structure and keratinized stratified squamous epithelium of the most superficial layer of the skin which provides an effective mechanical barrier against the insults of external environment. It is not possible, however, to consider the events occuring in a nuclear accident as separate phenomena, as the combined injury produced by the nuclear weapons results in multiple and complex effects on the human body. It is possible that the protective capacity of the skin will be deranged in both primary and secondary thermal injury, resulting in significant alterations of the skin, permitting an easier access of the externally deposited contaminants into the body. Burned, desquamated, and necrotic skin looses its integrity and provides an open route of entry to both radioactive and infectious insults to the internal organs. The main concern in preventing internal contamination through this route is the maintenance of the integrity of the skin.

Internal Contamination Through the Wounds and Injection into the Systemic Circulation

Direct access of radionuclides into the internal environment of the body is a result of thermal or traumatic injury in atomic bomb casualties, industrial or laboratory accidents or misadministration of the radiopharmaceuticals in diagnostic and therapeutic use of radioisotopes in the hospitals.

Primary injuries by the blast component of the nuclear weapon explosion usually occur in the proximity of the hypocenter and cause vascular and visceral damage without apparent damage to the skin. This type of primary traumatic injury is of no consequence for internal contamination. Secondary blast injuries, however, present a considerable internal contamination concern because of the contamination through the bruised, lacerated or cut wounds, as well as open fractures of the bones, multiple wounds caused by the fragments of the building material, glass splinters, wood or any other contaminated projectiles. These lesions present a complex problem because of coexistent complications of infection and internal contamination.

Intradermal or subcutaneous deposition of the fission products has been widely studied because of the therapeutic concern to eliminate radioactive isotopes from the contamination site without interrupting the integrity of the normal integument. The quantity of absorbed contaminant will largely depend on the depth of deposition, anatomic site of the skin, and size of the contaminated area. Some isotopes have relatively rapid translocation from the intradermal or subdermal site of deposition (iodine, strontium, cesium, tritium) whereas other isotopes have less avid absorption from the shallow dermal wounds (transuranic elements). The fate of the isotopes at the site of superficial deposition will largely depend on the healing processes or the complications of the superficial lesions (eschar, fibrous tissue, infection, draining ulcers). Translocation from the intradermal sites of contamination is mainly via lymphatic system and the ultimate deposition will depend on the physical and chemical nature of the isotope, solubility, particle size and organotropism. The management of the contaminated intradermal or subdermal wounds is still an area in which further investigative work is needed and should be addressed by the professionals with an experience in medical and surgical management of contaminated wounds (28).

Intramuscular deposition of radioactive isotopes has been widely studied and documented in the animal experiments and human accidental exposure. Some radionuclides will be completely and rapidly absorbed into the systemic circulation, e.g. strontium, iodine, tritium, while the others have slower translocation rate, e.g. transuranic elements. Retention in the various organic systems can be affected by the site of initial deposition of the radionuclide, e.g. intramuscular deposition of the actinides will predominantly result in the final incorporation in the skeleton, with a relatively low deposition in the liver, as compared with an intravenous injection. The other radioisotopes, such as iodine or osteotropic alkaline earths (calcium, strontium) will be much less affected by the site of their primary incorporation and will be ultimately deposited in the organs of their biologically specific avidity (thyroid, bone). Radioisotopes which are normally difusely distributed in the body fluids (cesium, tritium) will be largely unaffected by the site of their initial incorporation and the only consequence of their intramuscular vs intravenous administration will be the kinetics in the various compartments of the body.

Intravenous route of internal contamination results in the rapid incorporation of different radioisotopes in their respective target organs, as well as in the rapid removal through the renal, hepatobiliary and other endogenous systems of elimination. Retention and elimination of the various radionuclides will depend on their chemical form in plasma. Strontium ions for example are present in plasma in the protein-bound, complexed and free (hydrated) form and its elimination and reabsorption in the renal tubules will be determined by its chemical form. Complexed forms of osteotropic alkaline earth ions will be eliminated faster if they are in the ionized form. Other radioisotopes such as actinides which are preferentially incorporated in the liver and bone will be largely affected in their deposition and elimination as a consequence of intravenous versus other parenteral routes of administration. Intraveously injected actinides will be deposited in the liver in the higher quantities than after intramuscular administration, with lesser percent of bone deposition. Over 30 percent of intravenously injected plutonium will be rapidly eliminated, mostly via the gastrointestinal tract by the processes of hepatobiliary and endogenous elimination. The rate and amount of the liver and bone deposition of transuranic elements injected by intravenous route will depend on their polymerized form, acidity, presence of complexing agents and their valent state.

Intraperitoneal route of contamination occurs both in radiation accidents of nuclear weapon or industrial origin, as well as in therapeutic misadministation of the isotopes used in colloidal form in the treatment of metastatic deposits in the peritoneal cavity (Phosphorus-32).

Physical and Metabolic Characteristics of the Radioisotopes Common in Internal Contamination

Radioisotopes of medical concern can be classified in groups according to their physical or chemical properties, their metabolic behavior, and the pathogenesis induced in the target organs of their final incorporation. Classification is extremely complex because of the multiple factors that govern the metabolic pathways of each radioisotope. There may be significant differences in the metabolic behavior of the radioisotopes which are similar to each other, as well as metabolic similarities of the radioisotopes which have very little in common in their physical or chemical characteristics. Furthermore, radioactive isotopes of the same element can be entirely different in their behavior in the living organism. This makes their classification a complex and yet unresolved problem, and it can be addressed by considering each radioactive isotope a separate entity with a variety of different parameters that make each one a subject of individual consideration.

Together with those radioisotopes released by the explosion of nuclear weapons or industrial accidents, one has to consider health and therapeutic implications of those radionuclides which are of potential hazard in the cases of accidental hospital misadministration. Radioactive isotopes of over 40 elements are of interest for the medical implications of internal contamination. They include the radioactive isotopes of americium, arsenic, barium, calcium, californium, carbon, cerium, cesium, chromium, cobalt, curium, europium, fluorine, gallium, gold, hydrogen, indium, iodine, iron, lanthanum, lead, mercury, neptunium, phosphorus, plutonium, polonium, postassium, promethium, radium, rubidium, ruthenium, scandium, silver, sodium, strontium, sulfur, technetium, thorium, tritium, uranium, yttrium, zinc, zirconium, and mixed fission products.

Internal contamination by the fission products released in the explosion of nuclear weapons or after the accidents in nuclear industry, frequently occurs by the simultaneous contamination

with multiple isotopes, together with their products of radioactive decay. These mixed fission products will make a diagnostic assessment of the contaminated patient a challenging task, which necessitates diagnostic identification of the principal radioisotopes involved in internal contamination, so that proper therapeutic management can be instituted.

Americium

Two isotopes of americium are of importance in the internal contamination (Am-241 and Am-243). Am-241 (T½ PH = 458 years, T½ eff = 140 years) is a daughter product of plutonium, which decays to neptunium (Np-237) by the emission of high energy alpha particles. It also decays by a low energy photon emission (60 keV). Am-243 (T½ Ph = 7950 years, T½ Eff = 195 years) decays by alpha particles emission. Both isotopes most commonly occur in trivalent state, but may be present in oxidation states from II to VII. Internal contamination with americium most commonly occurs by the respiratory route or through contaminated wounds. Gastrointestinal absorption is negligible, but depends on the age and is higher in the young organism (35). Skin absorption is low but increases if the isotopes are present in a high acidity solution. Intramuscular route of contamination results in 10-60 percent of absorption from the site of incorporation, depending on the chemical form of americium. Target organs of americium are liver and bone (50-70 percent vs 20-30 percent of the retained dose, respectively) after parenteral administration. Skeleton is the primary target organ followed by the liver. There are reports of a high hematopoietic tissue, bone and gonadal malignant changes after intraperitoneal injection of americium in experimental animals (36).

Inhaled americium results in a preferential deposition in the lung, tracheobronchial lymph nodes, liver, lung, bone, and thyroid, with resulting tissue degeneration, fibrotic, and malignant changes. Human data on the metabolic fate of americium indicate that all americium compounds result in similar distribution in the liver (45 percent) and skeleton (45 percent) with the remaining 10 percent distributed in other tissues and excreta.

Californium

Among thirteen isotopes of californium only one (Cf-252) is of a potential internal contamination hazard. It is an alpha emitter with T½ of 2.6 years, with a photon emission of

43, 100, and 160 keV. This isotope is used in radiation oncology as a neutron source for intracavitary use (36).

Cf-252 is a serious external and internal radiation hazard, with metabolic properties similar to other transuranic elements. It is absorbed into the systemic circulation mainly through respiratory tract or contaminated wounds. Inhaled Cf-252 is mainly retained in the liver and bone with a significant retention in the pulmonary and tracheobronchial lymph nodes Intravenous or intramuscular administration of Cf-252 results in a 60 percent deposition in the skeleton and about 15 percent in the liver. Over 90 percent of Cf-252 initially deposited in the liver, is eliminated by the hepatobiliary secretion into the small intestine. Human exposure to Cf-252 has been reported after Cf-252 particle inhalation (23). Main biodistribution, internal dosimetry, pathology, and treatment data are however derived from the work on experimental animals.

Cerium

Two radioactive isotopes of cerium (Ce-141 and Ce-144) are of a potential significance as internal contamination hazard. Ce-141 (T½ = 32 days) decays by beta and gamma emission and is produced by neutron irradiation of stable cerium (Ce-140). Cerium-144 (T½ PH = 284 days) is a fission product of uranium and decays by beta and gamma emission. The route of internal exposure is mainly via inhalation. Gastrointinal absorption is negligible in humans and experimental animals (37). Critical organ for cerium-141 is the liver while cerium-144 is preferentially deposited in the skeleton. Inhaled cerium is preferentially deposited in the lung, whereas the critical organ for ingested cerium isotopes is the descending colon and rectosigmoid.

Cesium

Among twenty-one radioisotopes of cesium, only two are of medical significance as a potential internal contamination risk. Cs-137 (T½ = 30 years) decays by beta emission and its daughter product emission of photons (E = 662 keV) accompanies its spectrum of radioactive decay. Cs-134 (T½ = 2.1 years) decays by both beta and gamma emission, with multilple energy levels for each mode of decay.

Cesium-137 is a product of nuclear fission and has been studied in a great extent as a significant component of a radioactive fallout. As a metabolic homologue of potassium, it is uniformly distributed in the body and eliminated via renal system. Cesium enters systemic circulation either through respiratory or gastrointestinal system. Average biological half life in humans is 110 days in males, 80 days in females, and 60 days in children (38). Accidental contamination with Cs-137 has been declining due to its decreasing levels in the biosphere resulting from the reduced atmospheric testing of nuclear weapons.

Cobalt

Three radioactive isotopes of cobalt are of medical interest. Cobalt-60 (T½ = 53 years) decays by beta (0.31 MeV) and gamma emission (1.17 and 1.33 MeV). Cobalt-57 (T½ = 271 days) and cobalt-58 (T½ = 71 days) decay by gamma radiation.

Cobalt-60 is used in radiation therapy and in nuclear medicine diagnostic procedures for the studies of malabsorption and pernitious anemia by labelling vitamin B-12 (Schilling's test). Internal contamination with the isotopes of cobalt occurs mainly via inhalation of radioactive particles in the nuclear industry. There have been extensive studies on the metabolic properties of the isotopes of cobalt. Whole-body counting techniques have been used in biological half-time and distribution studies, together with the bioassay of urine. Intravenous administration of cobalt results in longer biological half-life than in cases of respiratory exposure. Intestinal absorption of radioactive cobalt is relatively low (5 percent), but increases in the presence of stable cobalt.

Critical organ for cobalt internal deposition is the liver (20 percent of the absorbed dose), after oral or intravenous administration.

Curium

Among 13 curium isotopes, Cm-242 (T½ = 152 days), Cm-244 (T½ = 16.7 years), and Cm-245 (T½ = 9300 years) are of medical significance. Main route of entry into the body is via respiratory system. 15-45 percent of inhaled curium is absorbed into the circulation and 10

percent is retained in the skeleton. Initial excretion of curium is via urine, while delayed excretion is equal between urinary and intestinal route, because initial deposition in the liver is slowly eliminated via hepatobiliary mechanisms. Bone retention of curium isotopes predominantly occurs on the mucoproteins of endosteal surfaces rather than in the bone minerals and is affected by the active growth of the bone, being particularly high in the areas of enchondral ossification (39).

Gold

Only one of twenty-four radioisotopes of gold (AU-198) is of interest in radiation toxicology. Au-198 (T½ = 2.7 days) disintegrates by beta and gamma decay. Its medical use is in the treatment of malignant effusions in the peritoneal, pleural, and pericardial cavities, as well as in the treatment of joint diseases by intracavitary or intraarticular administration in the colloidal form (40). It has been used in diagnostic studies in nuclear medicine studies of regional ventilation, in the form of aerosols. The first reticuloendothelial studies of the bone marrow were obtained in experimental animals with colloidal gold (Au-198), as early as thirty years ago (41, 42). It was also used in the liver scanning as a colloidal tracer (43). Its high gamma energy was a considerable limiting factor in its studies by the scintigraphic methods. It has also been used in the lymphoscintigraphic studies on experimental animals (43). Its therapeutic effect in the paliative treatment of the disseminated malignancies in the body cavities is mainly due to its beta particle radiation.

The metabolic behavior of radioactive gold largely depends on the route of entry into the body and on its form of administration (ionic or colloidal form). It is rapidly removed from circulation by the RES of the liver (80-85 percent) and spleen (5-10 percent). Gastrointestinal absorption of gold in noncolloical form is about 10 percent, with predominant deposition in the liver and spleen.

The main source of internal contamination with radioactive gold is therapeutic misadministration. Pathological changes caused by the intravenous administration of multimillicurie doses of Au-198 resulted in the bone marrow failure, with thrombocytopenia and cerebral hemorrhage with a fatal outcome. Hepatic failure was not a leading cause of death which was most likely due to the fast progression of platelet reduction leading to death before the liver function showed signs of deterioration.

Gallium

Gallium (Ga-67) is most commonly used in the form of citrate in the diagnostic image studies of malignant and infectious diseases. Ga-67 (T½ = 78 hours) decays by multiple gamma emissions. Its toxic effects mainly affect gastrointestinal tract, renal, hematopoietic, and lymphatic system. Toxic effects have been described in humans with the clinical manifestations of vomiting, exanthemas, proteinuria, anemia, and leukopenia. It is poorly absorbed after oral, subcutaneous, or intramuscular administration and the main route of contamination is by direct entry into the systemic circulation. There have not been been observed toxic effects with the current use of radioactive gallium (44).

Iodine

Ten radioactive isotopes of iodine are produced in a explosion of a nuclear weapon. Of all fission products of medical concern, radioisotope of iodine (I-131) represents one of the most common concern for the internal contamination. Other isotopes of iodine (I-132, I-133, I-134, I-135) are important in the early exposure to the products of nuclear fission. Iodine-131 (T½ = 8 days) is a principal cause of internal contamination in any nuclear incident and early exposure to the radioactive fallout or close proximity to the early fission products, I-131 decays by beta and gamma radiation. In reactor accidents iodine is a major cause of internal hazard concern because of its volatility and entry into the body via inhalation route (45). In nuclear weapon testing over 30 thousand curies of iodine-131 is estimated to be released for each kiloton of fission energy (46). In reactor accidents it has been estimated that over 20 thousand curies of I-131 were released into the atmosphere (47). Other routes of internal contamination are gastrointestinal absorption and cutaneous route of entry (intact skin, abrasions, wounds). Contaminated grassland after nuclear weapons atmospheric tests results in the major internal contamination hazard because of contaminated milk and dairy products. Marshall Islands experience indicated that radioiodine ingestion was the main hazard from the standpoint of internal contamination (48). In any case of suspected contamination with radioiodine it is essential to determine the thyroid incorporation by the thyroid bioassay for both gamma and beta radiation. In cases of significant external contamination, the early estimate of the thyroid uptake has to be interpreted with a caution because of the

contribution of the contaminated skin to the thyroid assay findings. Bioassay of I-131 body burden includes whole body counting and urinary excretion studies. Continuous follow-up thyroid monitoring should be routinely performed on all patients internally contaminated with radioiodine.

Mercury

Two radioisotopes of mercury (Hg-197 and Hg-203) are of medical significance. Hg-197 (T½ = 65 hours) has been used in the form of chloride for tumor scanning in the form of Hg-197 chlormerodrine for aerosol inhalation studies, renal scintigraphy, and spleen scanning. Its photon energy (E = 190 keV) makes it a convenient scanning agent, but its half-life and potential nephrotoxicity make its use relatively limited. Hg-203 has been less commonly used because of its half-life of 47 days and beta decay. Accidental contamination with Hg-203 in humans has been reported by the route of inhalation. Ingestion and transcutaneous absorption of mercury radioisotopes have been described as routes of entry in accidental internal contamination.

Phosphorus

Radioactive isotope of phosphorus (P-32) has been used in medicine as a tracer and therapeutic agent for over 45 years, since its production by deuteron irradiation of stable phosphorus. Its role in causing leukemia was reported soon after its initial use (49). P-32 (T½ = 14.2 days) is a beta emitter used in medicine as a therapeutic agent for treatment of polycythemia vera (PCV) and leukemia. Accidental internal contamination has been reported as a therapeutic mismanagement (50). It has also been used as a diagnostic agent in the detection of cranial, cutaneous, and breast tumors and it is still being used in the diagnosis of intraorbital malignant melanoma. Critical organ of phosphorus-32 incorporation is the bone which receives about 20 percent of phosphorus after ingestion or inhalation of its soluble forms. Accidental internal contamination with P-32 has not been reported in nuclear industry and main source of accidental exposures has been due to its medical use.

Plutonium

First in the chain of transuranic elements, plutonium is the most toxic substance known to man. Among 15 radioactive isotopes of plutonium two have been of importance as a potential internal contamination hazard.

Plutonium-239 ($T\frac{1}{2}$ = 24,400 years) is an alpha emitter with infrequent gamma decay. Plutonium mass of 16 grams contains one curie of radioactivity. Plutonium-239 produces a fission after exposure to slow neutrons (fuel for nuclear weapons and reactors). Plutonium-

been associated with the induction of bronchogenic carcinoma. Po-210 biodistribution has been extensively studied in uranium miners, as an isotope of uranium-radium chain. Its route of entry into the human organism is via inhalation, with negligible intestinal absorption and relatively small amount (2 percent) entering the body through the contaminated skin. Po-210 is an alpha emitter and its critical organs of deposition are the skeleton, lung, liver, muscle, kidney, and spleen (56).

Accidental internal contamination with Po-210 has been described in different incidents of inhalation exposure with bioassay and biodistribution studies, contributing to understanding of Po-210 distribution and excretion characteristics. Initial Polonium excretion is mainly through gastrointestinal elimination with urinary excretion being more singificant at late post-exposure intervals.

Radium

Radium-226 ($T\frac{1}{2}$ = 1620 years) is an alpha emitter, which decays to lead, after a series of radioactive elements in its chain of decay (radon-222, polonium-218, bismuth-214, lead-210). Its medical use has been primarily in the radiation oncology, as encapsulated radium containing needles, directly inserted into the tumor or by intracavitary or intraluminal deposition of radium sources in the proximity of the tumor (e.g.carcinoma of the cervix). Ra-226 enters the organism mainly via gastrointestinal route with 30 percent absorbed dose. Absorbed Ra-226 is predominantly eliminated by fecal route with a small fraction excreted through kidneys. Decay product of Ra-226 (Rn-222) is exhaled for a long time after deposition and provides a method for estimation of the quantity of Ra-226 in the body (radon breath analysis).

Radium-226 is a serious internal contamination hazard, with almost exclusive incorporation in the skeleton. There have been extensive studies on internal contamination with Ra-226 in the workers contaminated by ingestion of luminous paints containing radium-226. There have been reports over 60 years ago on clinical effects of internal contamination with radium in the dial painters who used to moisten their paint brushes with their lips and saliva and who subsequently developed osteogenic sarcomas. These early reports provided a significant contribution to understanding of the consequences of internal contamination and establishing

conventional criteria of permissible body burdens of other osteotropic radioisotopes. Long-term follow-up studies on internally contaminated dial painters resulted in a significant body of data concerning radium-induced pathogenesis of different types of malignant alterations of the skeleton, including osteogenic sarcoma, fibrosarcoma, carcinoma of the mastoid and paranasal sinuses, aplastic anemia, and leukemia. These changes have not been observed in persons whose cumulative doses of radiation in the skeleton were below 1000 rad (57). These studies included over 500 contaminated persons with a follow-up time of over 50 years.

Strontium

One of the most hazardous internal contamination radioisotopes is strontium-90 which is produced together with other five strontium radioisotopes in the process of nuclear fission of uranium. Sr-90 (ST½ = 28 years) decays by beta emission to yttrium-90, which is also a beta emitting radionuclide. Strontium-89 (T½ - 51 days) and strontium-85 (T½ = 65 days) are also of medical importance, but their implications have been of lesser concern in radiation toxicology than the effects of Sr-90. Strontium-85 has been used in the past in tracer and nuclear medicine diagnostic studies of the skeletal metabolism and bone scintigraphy.

Metabolism of radiostrontium has been widely studied in animals and humans, as a consequence of contaminated biosphere by the radioactive fallout in the nuclear weapons testing. The routes of entry of strontium are predominantly ingestion and inhalation but its access to the body fluids and target organs is rapid after absorption through the skin lesions. After its entry into the systemic circulation, strontium is rapidly deposited in the bone, first in its exhangeable fraction, followed by its deep incorporation into the nonexchangeable bone mineral structures, through the process of exchange with the stable calcium ions and physiochemical absorption in the crystals of hydroxyapatite. Amount of Sr-90 in the trabecular bone can be reduced by the therapeutic management which facilitates exchange of mineral salts between bone and plasma. However, once it incorporates into the nonexchangeable structures of the bone minerals, its therapeutic removal is impractical if not an impossible task, and the consequences of its bone retention, beta radiation and long half-life include genetic changes, leukemia and osteogenic sarcoma (58, 59). Strontium in the body behaves similarly to its metabolic homologue-calcium, but there are some quantitative

differences in their kinetics and ultimate quantity of their retention. Biological membranes (intestinal mucosa, renal tubular epithelium, placenta, and mammary gland) possess the ability of discrimination against strontium, favoring transfer of calcium ions. It is still controversial whether discrimination processes affect their transfer across the basal membrane in the bone tissue. Physiological factors, such as growth, nutritional, hormonal, and reproductive processes which affect the metabolism and homeostatic function of bone are of importance in determining the ultimate fate of this greatly hazardous product of nuclear fission.

Technetium

Technetium-99m ($T\frac{1}{2}$ = 6 hours) is a gamma emiting decay product of molydenum-99. Tc-99m is the most commonly used of all isotopes in nuclear medicine diagnostic studies. It decays by monochromatic gamma radiation to Tc-99 ($T\frac{1}{2}$ = 220,000 years). Misadministration cases of Tc-99m have been reported, but pathologic changes due to these incidents have not been observed.

Thorium

Thorium-232 ($T\frac{1}{2}$ = 1.39×10^{10} years) has been used in the past as thoratrast, a radiopaque substance for angiography studies. This particulate substance is rapidly phagocytized by the reticuloenothelial system of the liver, spleen, and bone marrow. Although it has been of value in delineating visualization of the blood vessels with a high degree of resolution, its presence in the body has been associated with the risk of angiosarcoma, hepatoma, osteogenic sarcoma, and pleural mesothelioma, which caused its replacement by the other diagnostic radioopaque agents.

Tritium

Tritium (H-3) is the only isotope of hydrogen which decays to He-3 by beta emission. Tritium ($T\frac{1}{2}$ = 12.3 years) is a normal constitutent of the atmosphere and biosphere produced by the fission of the radioactive elements in the earth crust, as well as by the cosmic ray irradiation of the stable nitrogen in the atmosphere. Nuclear weapons testing has resulted in an increased atmospheric concentration of tritium.

The routes of H-3 entry into the organism include inhalation, ingestion, and penetration through the skin. Ingestion of tritium in the form of tritiated water, results in rapid and complete absorption in the body fluids with diffuse distribution throughout the body. The body burden is monitored by the use of urinary bioassay, using liquid scintillation counting for the detection of its weak beta emission (E_{max} = 18 keV).

Accidental contamination with tritium has been reported in humans (60) where multicurie dose of tritium exposure was encountered, with the clinical symptoms of nausea, and exhaustion, leading to death due to panmyelocytopenia. Tissue sample analysis of tritium contamination casualties have demonstrated that tritium is present in the endocellular structural elements after internal contamination, together with its presence in the body fluids (61).

Uranium

Three isotopes of uranium are of the importance in medicine as potential internal contamination hazard. U-238 ($T\frac{1}{2}$ = 4.5 X 10^9 years), U-235 ($T\frac{1}{2}$ = 7.1 X 10^8) and U-234 ($T\frac{1}{2}$ = 2.5 X 10^5 years) are alpha, beta, and gamma emitters, with spontaneous fission below the level of criticality. Decay products of uranium isotopes include alpha emitting isotopes of radon (Rn-222 and Rn-219) which present internal contamination hazard by inhalation of radioactive particles in uranium mines. Uranium ore obtained in mines (U_3O_8) is concentrated and processed to ammonium diuranate (yellowcake), which is fluorinated and enriched for the use as the fuel for nuclear reactors or nuclear weapons. Uranium recycling is the process of obtaining uranium from the fuel dissolved in nitric acid, with the removal of fission products and transuranic elements. Uranium handling presents a hazard because of a possibility of chemical explosion in the process of uranium oxidation.

Uranium isotopes have different metabolic behaviour in the body, depending on their physical form. Ingestion of uranium isotopes results in a relatively low absorption (1-5 percent). The absorbed dose is rapidly excreted through kidneys. Other routes of internal contamination include inhalation or direct entry into the body fluids through the skin and contaminated wounds. The critical organ for uranyl salts (U - VI) is the bone, while uranous salts (U - IV)

are retained in the skeleton in much lesser quantity. Soluble euranium U-238 is rapidly eliminated through the renal excretion. Less soluble compounds of uranium particularly when enriched with U-234 and U-235 are primarily retained in the bone or in the lung if inhaled. Soluble uranium compounds cause mainly chemical damage to the proximal convoluted tubules of the kidneys (62), with resulting albuminuria, hematuria, hyaline and granular casts, azotemia, and tubular necrosis. Renal recovery even after the exposure to the high levels of uranium is quite common and additional exposures seem to cause less damage to the kidney after its initial recovery. Urine bioassay should be routinely performed in any case of exposure to uranium compounds.

Therapeutic Management of Internal Contamination

The principal goal in reducing radiation dose and pathologic effect of internally deposited radionuclides is prevention of the absorption from the contamination sites and elimination of absorbed radionuclides which are already in the blood stream or in their respective target organs. In all methods of therapeutic approach to the management of the contaminated patients, it is of utmost importance to institute therapy at early time after exposure. These procedures include the prevention and reduction of gastrointestinal absorption, with diluting and blocking agents, treatment with agents that cause decorporation of the radionuclides from the sites of internal deposition and their mobilization into blood stream, and therapy with facilitated excretion through the urinary, gastrointestinal, or respiratory system. Finally, medical management of internal contamination includes therapeutic administration of the chemical agents which facilitate the elimination of radioisotopes from the body by binding inorganic ions to nonionized complexes, which can be eliminated through the kidney when present in soluble forms.

Prevention of Gastrointestinal Absorption

Ingestion of various products of nuclear fission results in a rapid and high degree of their intestinal absorption into the systemic circulation with a consecutive deposition in their target organs. Reduction of the intestinal absorption of alkaline earth ions (calcium, strontium), cesium, cobalt, iodine, iron, gold, tritium, uranium, and radium is of a special importance in this therapeutic approach. Among the methods used for reduction of intestinal

absorption of medically significant radioisotopes and facilitation of their elimination via fecal route, most important are the gastric lavage, administration of emetics, ion-exchange agents, antacids containing aluminum salts, guluronic and manuronic acid salts of alginates, barium sulfate and sodium phytate.

Gastric lavage is the method of a high merit in the treatment of an early exposure by ingestion. It is performed by the insertion of naso or orogastric tube into the stomach which is repeatedly washed by introducing water or physiological saline into the gastric lumen and its aspiration until the aspirate is free of contaminating substance. All necessary precaution measures, including patient's positioning during the procedure should be applied for the complete gastric lavage and for the prevention of the aspiration of contaminated gastric contents into the respiratory system.

Use of emetics is a complementary method to gastric lavage, although they are frequently used separately. The use of emetics should be performed only after a careful diagnostic assessment of the contaminated patients, as they are contraindicated in patients in shock, altered consciousness, or after ingestion of petroleum or corrosive substances. Most commonly used emetics are apomorphine for the subcutaneous and ipecacuana derivatives for oral administration. A sound clinical knowledge of the management of direct and side effects of the emetic drugs is required in each case of their administration. Their application is best performed immediately after oral administration of 250 cc of water. Antiemetics act by direct effect on gastric mucosa and by the stimulation of the vomiting center in the medulla oblongata. Apomorphine is predominantly acting by stimulation of the vomiting center and should be administered in a single dose of 5-10 mg s/c, whereas ipecacuana derivatives can be used repeatedly until vomiting is induced (oral adminstration). Both agents are readily available. Clinical management of the potential side effects (nausea, weakness, tachipnea, tachicardia, hypotension) frequently don't require any specific treatment and could be treated by the symptomatic therapy.

Use of laxatives as a method of reducing internal contamination has been a common therapeutic approach. Laxatives are administered in the various forms, such as the rhinoleic acid releasing drugs which stimulate contractions of the small intestine (castor oil, cascara), saline purgatives which cause inhibition of radionuclide absorption by both insoluble salts

formation and cathartic elimination from the intestine, as well as by their hypertonicity, which causes water extraction from the intestinal mucosa. Detailed clinical diagnostic management is required prior to the use of laxative therapy as they are contraindicated in any case of undiagnosed abdominal pain, or acute surgical abdominal syndrome. Their use is also associated with multiple side effects, including heart dysrrhytmias, tachypnea, and dyspnea, intestinal irritation, exanthema, electrocyte imbalance and syncope, which have to be addressed by the appropriate symptomatic therapy.

Alginates

This group of ion exchange therapeutic agents are the extracts of brown seaweeds (pheophyceae). These compound act by their active ingredients -- alginic acids (guluronic and manuronic), binding radionuclides in the intestinal lumen and decreasing their absorption through the intestinal mucosa (63). The action of alginates has been most intensively studied in the comparative absorption of strontium and calcium through the intestinal mucosa. These cations are metabolic homologues with selective incorporation in the skeleton. Their metabolism, however is affected by the processes that control their transfer across the biological membranes, with favorable retention and transfer of calcium and discrimination against strontium. Alginates possess the ability to preferentially bind strontium ion in the intestine without much effect on the calcium absorption. This phenomenon has been utilized in the therapeutic management of internal contamination with ingested strontium (64), with a significant decrease of its retention in the skeleton. Alginates are used by oral administration. Their main disadvantage has been their high viscosity, although low viscosity preparations are available such as manucol SSLD (65, 66).

Ions exchange drugs which reduce intestinal absorption of ingested radioisotopes also include activated charcoal, sodium polystyrene sulfonate, biorex-40, ferric ferrocyanide. Their use should be performed with caution because of their side effects, including gastritis, anorexia, vomiting and diarrhea. Ion exchange resins can also interfere with the absorption of essential inorganic and organic nutrients by their binding and elimination from the intestinal lumen.

One of the forms of ferrocyanide used for decrease of intestinal absorption of ingested radioisotopes is Berlin blue (Prussian blue) which is particularly useful in binding and removal

This compound is commercially available in Europe. Its use in the United States is restricted to emergency situations in which a FDA investigational drug approval is required.

Aluminum containing antacids have been effectively used in therapeutic removal of strontium, with a highly significant decrease of Sr-90 intestinal absorption. Aluminum-phosphate administerred orally reduces strontium absorption by over 80 percent. Aluminum hydroxide reduces strontium uptake by 50 percent. There are no side effects associated with their therapeutic use.

Other drugs used for the elimination of ingested radionuclide from the digestive tract include barium sulfate, which is highly effective in reducing strontium and radium absorption and phytates which reduce absorption of calcium, iron, magnesium, and zinc ions.

Isotopic Dilution, Blocking Agents, and Displacement Therapy

Use of water in reducing tritium in the body fluids is a common therapeutic method, applied by oral or intravenous route of administration. Clinical assessment of each patient is essential in avoiding possible side effects of the fluid overload in the patients with cardiovascular or renal disease.

In the blocking agents therapy, radioactive iodine uptake is inhibited by the immediate administration of stable iodide shortly after accidental exposure (KI, NaI). This therapy should be continued for two weeks to allow elimination and prevent reuptake of radioactive iodine. FDA recommended dose is 130 mg KI for adults QID, and 65 mg QID for children.

Radioactive strontium uptake can be reduced by the administration of stable strontium compounds (lactate, gluconate). Intestinal absorption of radiostrontium can be significantly reduced by the oral administration of phosphates which reduce over 60 percent of strontium absorption. This effect is sometimes counterbalanced by increased tubular reabsorption of strontium if phosphate content is elevated in extracellular fluid.

Tubular reabsorption of strontium increases after intravenous administration of phosphate. This factor reduces the net effect of diminished skeletal retention of strontium by the high phosphate content in the digestive system (67). Parenteral administration of phosphate can be used in treatment of internal contamination with soluble radioactive phosphorus (P-32).

Calcium salts have been used in reducing intestinal absorption of radioactive strontium (Ca-lactate, Ca-gluconate). Other stable cations (potassium, zinc) are rarely used as potential agents in management of Zn-65 or K-42 internal contamination.

Therapeutic agents for decorporation and mobilization of the organotropic radioisotopes include hormonal preparations (PTH, corticosteroids, calcitonin), propylthyouracic (PTU) and methimazole (MI), diuretic, expectorants, perchlorate, ammonium chloride. Parathormone has been used in different species of experimental animals to enhance bone resorption with subsequent release of incorporated osteotropic radionuclides (calcium, strontium, phosphorus, radium). It has been demonstrated that physiological processes resulting in increased catabolic processes in the skeleton produce significant reduction of the amount of incoprorated bone seeking radioisotopes. These effects have been observed in lactating animals, whose skeletal uptake of calcium and strontium was reduced by over 50 percent after catabolic processes of the skeleton induced by lactation. This reduction of the bone mass and demineralization of both exchangeable and nonexchangeable fraction of the skeleton was observed regardless of hyperphagia in the lactating animals. Mechanism of lactation induced demineralization of the skeleton was postulated to be PTH induced mobilization of the bone minerals to satisfy requirements of the organism in negative calcium balance. These data were observed in different animal species including dairy cattle, which oscilate between normal and demineralized exchangeable bone in each reproductive cycle (67). PTH induced demineralization of the bone, however does not affect retention of bone seeking transuranic elements. Mechanisms of incorporation of actinides is entirely different form the processes which govern metabolic behavior of bone seeking alkaline earth ions in the skeleton. Retention of americium (Am-241) was found to be elevated under the influence of lactation, whereas PTH had no effect on the retention of plutonium (Pu-239) in the skeleton. Actinides are not controlled by PTH regulated homeostatic processes, like alkaline earth ions and PTH induced bone resorption results in their increased retention because of increased availability of the incorporation sites at the of cesium (Cs-137).

resorbing surfaces of the bone where some actinides are bound to syaloproteins of the actively resorbing endosteal surfaces (68).

The influence of corticosteroid hormones (prednisone, cortisone, dexamethasone, methylprednisolone) have been studied in various experimental models with an attempt to evaluate their use in mobilization of the incorporated bone-seeking radioisotopes. There was no significant effect of corticosteroids in the metabolic behaviour of transuranium or alkaline earth isotopes in the bone, regardless of the catabolic processes induced in the skeleton by the long-term use of corticosteroids.

Propylthiouracil (PTU) and methimazole (MMI) decrease synthesis of thyroid hormones (T3, T4) by their inhibitory effect on the iodide oxidation. These antithyroid drugs have not gained popularity in antagonizing radioiodine uptake by the thyroid, because of their complex metabolic effects on the radioiodine in the kidney and liver, as well as numerous toxic side effects. Other antithyroid drugs (thiocyanate) are not of practical use for radioiodine elimination because of questionable effects and toxic reactions. Of all compounds used for the inhibition of thyroid uptake of radioactive iodine, stable iodide is the drug of choice for competitive inhibition of I-131 incorporation.

For the mobilization of radiostrontium from the body, ammonium chloride was found to be of certain benefit in reducing body burden of Sr-90. Its toxic effects, however, make it less than an ideal drug for strontium decorporation (gastritis, hepatitis).

Diuretic therapy with various conventional agents has been used in various studies on excretion of internally deposited radioisotopes. The complex metabolic effects of diuretic drugs with the need of meticulous monitoring of the electrolyte and ECF metabolism, make diuretic therapy of internal contamination still an unexplored area. Ethacrinic acid is the only diuretic agent currently recommended for the excretion of the alkaline earth isotopes.

Treatment of the patients exposed to the radioactive particles via respiratory route of contamination includes administration of the drugs which reduce viscosity of endobronchial mucus and various mucolytic drugs acting on mucopolysacharides and nucleoproteins in respiratory tree, thus making its contents mobilized by expectoration. The results of testing

these agents (pancreatic dornase, triton, tween-80, F-68, etc.) have been unsatisfactory in reducing the uptake of inhaled radioisotopes from the lung.

Treatment of Internal Contamination with Chelating Agents

Complexing agents have been used in the treatment of internal contamination in experimental animals and accidentally exposed humans with more success than other therapeutic modalities. The elimination of radioactive isotopes by chelation therapy is based on the ligand ability to form nonionized ring complexes with inorganic ions, which are subsequently excreted by the kidney. Treatment with chelating agents should be instituted as soon as possible after internal contamination, before the radionuclides are retained in their target organs. Hydrophylic nature of these agents makes them ineffective in reaching the isotopes incorporated in endocellular environment and there are numerous current studies concentrated on the synthesis and production of lypophylic chelating agents for their potential use in mobilization of radionuclides from the cells and excretion by the kidney.

Effect of chelation therapy with various complexing agents has been an area of extensive experimental and clinical research. Among numerous chelating agents tested in the experimental and clinical trials, only a few remain of practical use at the present time.

EDTA (ethylene diamine tetra acetic acid) has been used in animal experiments and human medicine for the treatment of poisoning with various inorganic compounds. Its use in the therapy of saturnism has been of practical therapeutic benefit as well as in treatment of zinc, copper, cadmium, chromium, manganese, nickel, as well as in internal contamination with transuranic elements (69). Parenteral administration of EDTA results in its binding of stable calcium with resulting consequences of hypocalcemia (tetany) and toxic side effects, among which nephrotoxicity is the primary complication with a potential fatal outcome. EDTA can be used as Ca-EDTA or Na-EDTA. Na-EDTA dose for intravenous administration is 75 mg/kg, BID not exceeding total dose of 550 mg/kg in the entire therapeutic regimen. Intramuscular administration (75 mg/kg, TID) should be used with local anesthetic because of tissue irritation and pain at the injection site. Intravenous route of administration by infusion in physiological saline or 5 percent glucose in water is preferred method of administration. Renal function tests and urinalysis should be performed before treatment, as EDTA therapy is

contraindicated in patients with renal disease. Na-EDTA is used in a lower dose (50 mg/kg) as physiological saline or 5 percent glucose not exceeding 300 mg per treatment period of 6 days. Oral or intramuscular administration is not used. Its use is contraindicated in renal and hepatic disease.

DTPA (diethylene triamine pentacetic acid) is more effective than EDTA in therapeutic removal of radioisotopes common in internal contamination. It is used in the form of Ca-DTPA and Zn-DTPA. Ca-DTPA is administered as intravenous infusion (1000 mg in 250 ml of physiological saline or 5 percent glucose), for maximum of five consecutive days. DTPA can be obtained in the USA as an investigational new drug from the US Department of Energy, Office of Health and Environmental Research, Human Health and Assessment Division, Washington, D.C., or React/TS Center Oak Ridge, TN. DTPA administration is contraindicated in leukopenia or thrombocytopenia, renal disease, hypertension, or pulmonary disease (if used as inhalation therapy). Zn-DTPA can be used in the same dose as Ca-DTPA by intravenous or inhalation route and is less toxic than Ca-DTPA. Na-DTPA is not used because it chelates calcium with resulting hypocalcemia and tetany. DTPA is currently the most effective agent in treatment of internal contamination with transuranic elements, particularly plutonium and americium. DTPA does not produce toxic symptoms if used in recommended doses in either intravenous or inhalation route of administration.

Other agents for the treatment of internal contamination include (dimercaprol (BAL) which has been effective in contamination with radioactive mercury (Hg-197, Hg-203). It is used by intramuscular administration in the dose of 2.5 mg/Kg for ten consecutive days. It has been successfully used in the treatment of intoxication with arsenic, mercury, lead, gold and has higher efficacy in copper removal in hepatolenticular degeneration, than other chelating agents (70). However, its use in the treatment of internal contamination with radioisotopes is restricted because of the superiority of other chelating agents (EDTA, DTPA).

DFOA (deferoxamine) has been successfully used in the removal of excess iron in various metabolic iron storage disease and in iron intoxication. DFOA has been successful in elimination of plutonium-239 in acute internal contamination. It can be administered by oral, intramuscular or intravenous route. Its therapeutic effect is enhanced if given together

with DTPA (71). Its use requires caution because of potential side effects, including exanthema, tachicardia, and hypotension.

Other chelating agents studied in animal experiments and accidental human exposure to the radioisotopes of internal contamination include TTHA (triethylene tetraamine hexaacetic acid) which has similar effect in the treatment of internal contamination as DTPA, with a distinct advantage of being effective in the lower dose after oral administration than other chelating agents (72). This agent has been extensively studied in an attempt to replace intravenous infusions by the more practical, oral administration of chelating agents.

BAETA (bis dicarboxy methyl amino diethyl ether) is another chelating agent which showed potential promise for the treatment of internal contamination. It has been found that this agent is superior to EDTA but less effective than DTPA in elimination of actinides (73).

Treatment of internal contamination is presently limited to few therapeutic agents, with considerable problems associated with their use. Present therapeutic modalities are still unsatisfactory, particularly in removal of the radionuclides already incorporated in their respective critical organs. In the removal of the most hazardous radionuclides of the transuranium series, DTPA is clearly superior to other chelating agents. Its use however is limited because it is not commercially available, its administration has to be performed by the qualified personnel, it is effective only in the early contamination without affecting incorporated radioisotopes and its strong hydrophylicity prevent it from reaching intracellular environment. It is not of practical use in the treatment of mass casualties of internal contamination, although it has distinct benefits in the treatment of sporadic contamination cases in the presence of available medical facility. These factors have contributed to continuous investigational efforts to produce new chelating agents. Derivatives of paraaminocarboxylic acid (PACA) have been studied in an attempt to synthesise adequate lipophylic agents (chelons) for intracellular binding and removal of incorporated radioisotopes, with their potential use by oral, rectal or depot administration in the treatment of mass casuaaties of endemic or epidemic proportions. Other agents currently studied as a potential addition to the treatment of internal contamination, include several synthetic catecholamides, various phospholipid compounds (liposomes) for encapsulation of the radiotoxic substances and natural chelates isolated from the cultures of various

microorganisms. Their place in the medical management of internal contamination is yet to be determined in experimental and clinical trials.

Increasing possibility of accidents in nuclear industry, potential use of tactic nuclear weapons by the Third World countries or even by the various terrorist groups and exposure of the personnel required to recover an area after nuclear bomb detonation, warrant further investigations of the medical management of internal contamination. Apocalyptic consequences of an overall strategic nuclear exchange involve the questions of universal concern and extend far beyond the domain of the primary patient care.

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