Minisymposium: Metal Toxicity and Therapy, including Environmental Aspects

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Metals — Requirements, Surveillance and Therapy

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Now, more than at any time in the past, man's destiny is more subject to his own control and influence. This is true for many facets of civilisation, not the least of which is man's bioinorganic chemistry. It has been widely established that all metals are potentially harmful and yet many of these same metals, in trace amounts, are absolutely essential to our health, safety, and longevity [1].

In order to assess our requirements for trace metals, to ensure adequate surveillance of the trace metal constituents of our foods, and to design ligand drugs to remove excesses of undesired metals, it is necessary to have a thorough knowledge of speciation. This is the key to understanding many of the important bio-inorganic mechanisms which occur *in vivo.* A realisation of this fact has given an impetus to develop new techniques for speciation analysis, and national and international bodies have been set up to examine all aspects of trace metals *in vivo.*

Essentially, their tasks involve assessing (i) how the metals pass from soil into plants and animals and thence into man's diet, (ii) the imbalances which may well be associated with disease in man, and eventually, (iii) the restoration of trace metal balance by appropriate therapy. All facets of this trace metal food chain are examined in the following five lectures.

1 D. R. Williams and B. W. Halstead, *Journal of Toxicology,* at press [1983] No. 7. 'Chelating agents in medicine'.

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Plutonium *in vivo* and Drugs to Remove it from Man

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Plutonium-239, an important component of the nuclear fuel cycle, can enter the human body by ingestion, inhalation or by absorption through the skin or a wound. If sufficient quantities are deposited in the body the emitted alpha-particle radiation may induce serious toxic effects, including bone and other tumours.

Gastrointestinal absorption is influenced by age, physiological and dietary factors, but in adults it appears unlikely to exceed 0.1%of the ingested amount. Absorption through the intact skin is probably less than 0.01%. However, depending on its chemical form, the absorption of inhaled material from the lungs may range from <5 to 100%. Following entry into the systematic circulation, plutonium deposits to more than 80% in the skeleton plus liver of all the species studied. Skeletal retention of plutonium is prolonged with half-times equal to, or longer, than the normal life span of the species; for man a half-time of 100 years is assumed. In liver both the uptake and the retention show marked species variations. Some species, *e.g.* dog and chinese hamster, show very prolonged, if not infinite, retention while in others, *e. g.* rat, tupaia, macaque and baboon, more than 90% of the liver plutonium is lost with half times ranging from a few days to a few months. Into which category man falls is uncertain.

Complex formation with biological ligands plays an important role in plutonium metabolism. In blood, plutonium occurs as the complex with the ion-transport protein transferrin and this complex may also play a role in cellular uptake. Within the cells of liver and other tissues plutonium is largely deposited in lysosomal structures and within these structures the metal may be associated with ferritin [1].

Human exposure to plutonium comes principally from the metal which has been released into the atmosphere by nuclear weapon testing. Autopsy data suggest that for the general public the total body content of plutonium lies between about 15 and 50 picograms (35 to 110 milliBequerels). Exposure to higher levels of plutonium may occur amongst workers in the nuclear industries. During the past forty years several hundred workers have acquired body burdens of plutonium ranging from some tens of nanograms to about 4 mg and the health of these people is being carefully monitored. To date no late effects which can confidently be ascribed to plutonium toxicity have been observed [2].

During the past thirty years various treatment regimes designed to reduce the risk of late effects arising from internally deposited plutonium have been proposed; these are all based on the assumption