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.

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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 that acceleration of the normally very slow excretion of the metal will lead to a proportionate reduction in the risk of late effects. This hypothesis is not yet fully proven. Many substances have been tested for their ability to remove plutonium but only the polyaminopolycarboxylic acids, especially diethylenetriaminepentaacetic acid (DTPA), have proven to be really effective. DTPA, as the Na_3Ca- or the less toxic Na_3Zn salts, has been used widely and successfully in man and this substance is the current agent of choice for the treatment of plutonium contamination in man. Toxicity presents little problem and the possibility of serious depletion of essential trace metals seems to be small, especially when the Zn salt of DTPA is used. The efficacy of DTPA treatment decreases with increasing time after exposure to plutonium and it has only limited ability to remove inhaled insoluble plutonium from the lungs. Removal of fixed bone deposits is also difficult [3]. Normally DTPA is administered by intravenous injection or infusion, but recently inhalation of an aerosol [4] or oral administration [5] have been shown to be effective in animal studies.

The search for more effective agents than DTPA continues. Much interest was shown in a lipophilic derivative of DTPA — Puchel — which, unlike the ionized DTPA species, was able to enter cells. However, despite promising early results, this substance proved to be no more effective than DTPA and to be rather more toxic [6]. Recently new types of linear polycatechoylamino ligands (LICAM's) have been developed which are designed specifically to complex plutonium. Initial studies suggest that these may represent an interesting new approach to plutonium removal, but that their true therapeutic advantage over DTPA for human treatment remains to be assessed [7].

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Speciation Studies in Natural Waters

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The central theme of man's quest for an understanding of the importance of metal ions in the environment is 'bioavailability'. We may be concerned with problems such as the increased leaching of heavy metals from soils due to acid rain or the return to man of high level radioactive waste eluted by ground waters from its deeply buried container.

Unfortunately, the total concentration of a species is seldom a measure of its bioavailability [1]. Rather, a knowledge of whether an element is likely to form species that are in appropriate forms, either to be transported from one system to another or to take part in processes within systems is required. The study of 'speciation' (meaning the existence of the individual physicochemical forms of an element which make up its total concentration) is therefore becoming increasingly important.

An experimental speciation study can prove a difficult task. Coarse separations of molecular from colloidal species make use of techniques such as ion-exchange, ultrafiltration, dialysis and gel chromatography [2]. More detailed analyses can be achieved by anodic stripping voltammetry for aqueous species [3] and gas chromatography for volatile species. Ion-selective electrodes can measure activities of metal cations and small inorganic anions directly [4]. However, problems such as the high degree of skill often required, the disturbance to equilibria, nonspecificity and insensitivity at the concentrations occurring in the environment, often severely limit the usefulness of these experimental approaches.

Computer simulation of equilibrium systems is becoming increasingly capable of providing useful information concerning speciation. The general requirements of such a study are the total concentrations (or free concentrations, if available) of all components and the formation constants and solubility products of complexes and solids formed from the components. *A priori* predictions of extent of complexation cannot merely be based on the size of formation constants so computer programs (such as GEOCHEM [5], ECCLES [6] and WATEQ [7]) that can solve large systems of non-linear equations, have been developed.

Total concentrations can be determined at very low levels using such techniques as flame emmission and atomic absorption spectrophotometry and radiometry [8]. Also, critically evaluated formation constants and solubility products are becoming available for an increasingly large number of complexes and of solids [9].