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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D3

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].

The assumption that an environmental system is at equilibrium is only valid if equilibrium between all species is reached very quickly. However, if some reactions are very slow, the equilibrium between the species involved can sometimes be ignored. The extent to which reactions with intermediate rates are a problem depends on the application.

The inclusion of equilibria involving complex macromolecular species such as fulvic and humic acids has been either avoided or approximated by making use of conditional stability constants [10, 11]. However, a new method, whereby concentrations of many individual metal binding sites on the macromolecules can be estimated from 'random' computer generated fulvic acid molecules, does provide more detailed insight into the mode of metal binding by these substances [12].

Equilibrium calculations on large systems have received widespread application. The sea has been studied for many years [13, 14]. Fresh water, lakes and river systems have been investigated [7, 10] as well as the so-called 'soil solution' [15]. Other important areas include human blood plasma [6] and plant xylem fluid [16].

Computer models, nevertheless, must be judged on their ability to predict real behaviour [17]. They should be supported, wherever possible, by experimental investigations, the direction of which can often be indicated by the results of the model itself. The current trend of investigations into the identity of important naturally occurring ligands and the determination of their formation constants with metal ions needs also to continue unabated.

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D4

Copper Complexes: A Physiologic Approach to the Treatment of 'Inflammatory Diseases'

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Copper is an 'essential' metalloelement and as such it is required for life. Since none of the essential metalloelements can be synthesized *in vivo* it is required that they be obtained in the diet. If, following absorption, copper is not utilized immediately in the synthesis of copper-dependent enzymes it is either stored in the liver or excreted in a homeostatic fashion.

It is well established that copper-dependent enzymes are required for cellular utilization of oxygen; dismutation of superoxide; cross-linking of collagen and elastin; synthesis of dihydroxyphenylalanine, melanin, norepinephrine, and epinephrine; metabolism of monoamines; and mobilization of stored iron for hematopoeisis. Other biochemical processes which are less well understood concerning the involvement of copper are: modulation of prostaglandin synthesis, lysosomal membrane permeability, modulation of histamine activity, angiogenesis, enhancement of synaptic vesicle attachment to neuronal plasma membranes, uptake and release of monoamines by synaptosomes, and activation of brain adenylate cyclase.

A 2 to 3 fold increase in plasma or serum copper concentration is observed as a general response to infectious, inflammatory, and stress related diseases. It is well documented that blood copper concentrations increase in arthritic diseases, seizures, and neoplastic diseases and it is likely that there is a similar elevation with ulcers and diabetes. These elevations are viewed as a general acute phase physiologic response which facilitates remission. In the event that this physiologic response is impaired remission does not occur.

Copper-containing components in blood are: ceruloplasmin which contains 6 atoms of copper and has a molecular weight of 132,000, a copper–albumin complex with a molecular weight of 69,000, and a variety of amino acid complexes with molecular weights in the range of 300 to 400. While there is