Introduction: Mechanisms of Metal Toxicity Special Issue

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Metals are ubiquitous in our environment, and they are essential for humans and, in fact, for all forms of life. Even though a variety of metals is necessary in biological systems, they are usually required only in trace amounts and can be toxic, if not fatal, in excess. Metals are probably the first toxins known to humans. Human use of lead began prior to 2000 BC when it became readily available from ores as a byproduct of silver smelting. The early Greeks and Romans documented both the toxic as well as the potential healing effects of metals. In 370 BC, Hippocrates described abdominal colic in a worker involved in the extraction of metals. Theophrastus of Erebus (370−287 BC) and Pliny the Elder (23−79 AD) described the pernicious effects of arsenic and mercury on miners and smelters.

Metals have been used throughout most of human history to make various utensils, machines, jewelry, etc. Many of the metals for these uses were obtained through mining and smelting, activities that greatly increased their distribution throughout the environment. More recent applications of metals in industry, medicine, and agriculture have further increased our exposure, not only for those workers involved directly in working with metals in their various forms but also consumers of the products and the general public through environmental contamination. Thus, the role of human activity in the redistribution of metals in the environment is now well recognized, and it is clear that environmental metal contamination reflects not only natural sources but also significant contributions from mankind's industrial activities.

Of the more than 80 elements classified as metals, only about 30 have so far been reported to produce any type of toxicity in humans. Of course, reports on the toxicity of some of the rarer or lesser known metals may emerge as exposures increase due to new applications in drug therapy, microelectronics, nanotechnology, or other evolving technologies. Exposure to metals can lead to very serious toxicological consequences. These effects depend primarily on the type of exposure (ingestion in water, foods, medicine, etc.; inhalation; dermal absorption), the form of the metal (elemental, salt, particulate, vapor, and amalgam), the dose, and the length or frequency of exposure.

The principles of pharmacology and toxicology such as dose−response and individual sensitivity also are applicable to the toxicity of metals. The observed effect is a function of the dose or some estimate of overall exposure based not only on the concentration and amount of the metal but also on the exposure duration. Thus, an important determinant of the dose−response relationship is the time that the metal resides in the body, often measured as the half-life of the metal (the time to excrete half of the accumulated amount). These principles are particularly important in light of the fact that, in addition to acute toxicities, many metals exert subtle, chronic, long-term damage for which the cause-and-effect relationships are much less obvious. Examples include decreases in an individual's mental performance due to lead exposure or the carcinogenicity of chromium and arsenic.

For a metal to have its biological effect, be it beneficial or toxicological, it must cross the cell membrane and enter the cell where it then can bind either reversibly or irreversibly to a cellular target and thereby alter specific biochemical processes. Common mechanisms by which toxic metals may act include inhibition of enzymes, disruption of the structure and/or function of subcellular organelles, interaction with DNA leading to mutagenesis or carcinogenesis, covalent modification of proteins, displacement of other critical metals in various metal dependent proteins, and inhibitory or stimulatory effects on the regulation of expression of various proteins. Competition between metals for complexation sites in proteins involved in electron transfer reactions may lead to toxicity. Some metals act to generate free radicals, which lead to damage and subsequent degradation of critical cellular proteins, membranes, and organelles. The result of these diverse mechanisms is damage to various organs including the kidney, nervous system, respiratory system, endocrine, and reproductive systems.

Unlike other toxic substances, metals can neither be created nor destroyed by humans. However, their forms may be changed, thereby altering their biological availability, activity, and consequently, their toxicity. As already indicated, the targets for metal toxicity are generally cellular molecules, macromolecules, membranes, or organelles, and the toxic effect of the metal usually involves the initial interaction of the free-metal ion with the toxicological target. Thus, protection against metal toxicity may occur by the formation of nontoxic metal−protein complexes with various proteins such as metallothioneins. Toxicity is also influenced by other factors such as age, with individuals at both ends of the life span, either young children or elderly people, generally believed to be more susceptible to metal toxicity than middle-aged adults. For those metals that produce hypersensitivity reactions such as contact dermatitis, another important toxicological variable is the immune status of the individual exposed to that metal.

In this issue, we feature 17 papers on various aspects of metal toxicity from academic and governmental scientists who are experts in the field. These papers include a mixture of original research articles, perspectives, and reviews. The papers deal with environmental, pharmacologic, and occupational exposures to a variety of different metals including nickel, cobalt, chromium, copper, iron, arsenic, cadmium, uranium, zinc, and platinum. They also deal with a number of different types of toxicity including contact dermatitis, neurotoxicity, and chemical carcinogenesis. The overall focus of all of the papers is the chemical mechanisms of toxicity, as would be expected for articles published in *Chemical Research in Toxicology*. The articles span a range of mechanisms, stretching from the interaction with amyloid peptides to effects on transcription factors and an array of different target tissues including skin, brain, arteries, lung, bladder, kidney, and bone.

Two papers deal with studies on the mechanisms by which chromium and cadmium interact with transcription factors involved in signal transduction leading to various types of toxicity in target tissues and organs including lung, kidney, bone, and airway (Kothinti et al. (DOI: 10.1021/tx900370u) and Nemec et al. (DOI: 10.1021/tx900365u). Three papers involve studies on the mechanisms by which various forms of chromium cause DNA damage leading to carcinogenesis (Gremaud et al. (DOI: 10.1021/tx900362r); Macfie et al. (DOI: 10.1021/tx9003402); and Wise et al. (DOI: 10.1021/tx900363j)). The

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mechanisms by which zinc chromate (Holmes et al. (DOI: 10.1021/tx900360w)) and depleted uranium (Xie et al. (DOI: 10.1021/tx9003598)) cause transformation of human lung cells are the focus of two articles, while another looks at the role of the DNA damage response proteins p53 and p21CIPI/WAFI in the induction of micronuclei following the exposure of human fibroblasts to the environmental carcinogen sodium arsenite (Salazar et al. (DOI: 10.1021/tx900353v)). Somji et al. (DOI: 10.1021/tx900346q) investigate the degree of squamous differentiation and the expression of keratin 7 in a human urothelial cell line exposed to cadmium and characterize the phenotypes and genotypes of the cadmium transformed cells, while Munk et al. (DOI: 10.1021/tx900372p) describe a series of photoactivatable *cis*- and *trans*-diazido platinum anticancer compounds and the relationship between their stereochemistry and phototoxicity. Various aspects of metal allergy, from exposure and epidemiology through genetic and clinical implications are reviewed by Thyssen and Menné (DOI: 10.1021/tx9002726), while Brewer (DOI: 10.1021/tx900338d) considers the risks of and potential mechanisms for the heightened toxicity of copper and iron in the aging human population. The potential role of oxidative stress in arsenic-induced carcinogenesis is reviewed by Kitchin and Conolly (DOI: 10.1021/tx900343d) who also discuss the development of biologically based dose−response models and their use in risk assessment. The crucial role of the interactions of copper with amyloid beta peptides in the neurotoxicity of Alzheimer's Disease and the role of human serum albumin in protecting against this amyloid beta-mediated neurotoxicity of copper are presented by Rózga et al. (DOI: 10.1021/tx900344n) and Rózga and Bal (DOI: 10.1021/tx900358j), respectively. Finally, studies on the interaction of metallothionein and its zinc and cadmium complexes with nitric oxide and the possible role of these complexes in protection against metal ion toxicity are investigated (Zhu et al. (DOI: 10.1021/tx900387k)).

The issue of metal toxicity is a complex one, and we have much more to learn about the epidemiology, exposures, dose−response relationships, mechanisms of toxicity, and factors altering human susceptibility to metal toxins. Questions regarding whether similar mechanisms are observed depending on the form of the metal, the target organelle, or the route of exposure are of great interest and leave a very wide and deep field for their investigation. Also, the role of genetics in the various types of responses and the threshold levels of exposure leading to various responses will also be fertile fields for investigation. This is certainly an area of human toxicology where much experimentation and new insights are required. We hope that this collection of papers will not only serve to introduce the topic to new investigators in the area but also serve as a useful reference for those who are already involved in studies in this field. We also hope that it will serve as a stimulus to those in the field, as well as others, to develop new approaches to investigate the mechanisms by which metals serve as toxicants and to develop approaches that can be used to protect against their toxicities.

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Associate Editor

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