The Carcinogenicity of Metals

Human Risk through Occupational and Environmental Exposure

Issues in Toxicology

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I should like to dedicate this publication to my grandchildren, Emma, Rosie, Molly, Caroline and Christopher. Whatever aspirations they may develop in the future, I hope that their endeavours will bring personal rewards and satisfaction as have come my way in the study of metals over more than 40 years.

This volume is also dedicated to my wife, Veronica, who has given me loving support and friendship throughout my endeavours.

I acknowledge with sincere gratitude the fruitful conversations and constructive criticism provided by many friends and acquaintances at the former Charing Cross and Westminster Medical School, Birkbeck College and the British Industrial Biological Research Association.

Foreword

The ancient Egyptians had knowledge of the dangers of antimony, copper, crude arsenic and lead, and, in a number of cultures in the last three millennia, minerals have been used as poisons. A more clearly defined role for the widespread effects of these elements on human health and in disease states has been identified and characterised during the last two centuries. Initially, the need for a particular element was often discovered by observations of deficiency states in particular locations (iodine for goitre, as an example) but as a wider interest in comparative epidemiology developed, conditions induced by large local excesses of particular minerals were also identified and could be attributed to the effects of this excess (arsenic in drinking water in central Europe, say). Observations relating to the effects of therapeutic interventions had also shown that mercury and its salts, gold and silver, all used in manner that was hoped to confer benefit, may all cause evident human toxicity.

That we need many minerals in varying amounts is clear for reasons set out in early chapters of this book. As with vitamins, it is also clear that an excessive intake can be harmful – and that acute and chronic toxicity may result from exposure to excessive intake. These exposures may occur for a number of reasons and from varied sources, many of which have been recognised in comparatively recent times.

Occupational disease (wrist drop in painters) was recognised as a marker of toxic exposure and helped to define the cause of the toxic effects seen. In a clear historical example, mining of uranium-bearing ore in Schneeberg (Germany) and Jachimov (Czechoslovakia) both for metals and the manufacture of uranium dyes had been carried out for centuries and was known to be associated with lung disease – both pulmonary fibrosis and carcinoma of the lung, although this distinction was not evident to contemporary observers when the link was published in 1879. The development of industry and of industrial processes together with the gradual development of health care relating to those

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working in industry and better record keeping relating to workers and the local environment (an often undervalued element in identifying causality in disease processes) made clear that industrial development has produced well-defined problems such as the presence of organic mercury compounds in effluvia (Minamata Bay).

Associations of a different kind, relating to long-term exposures and to exposures to levels of toxin that did not produce acute illness or evident direct toxicity, were harder to identify. Although potentially carcinogenic actions of minerals were often investigated after singular associations between occupations and uncommon tumours had been identified, modern methods of diagnosis and record keeping were needed to provide the means to question potential causality between exposures and common tumours. These associations would often promote a search for pathogenetic mechanisms by experimentation.

Epidemiological research is a valuable weapon in identifying apparently causative factors in disease. Although causes may be defined in a number of ways, in pragmatic terms it is clear that if the elimination of a causal factor results in a change in disease incidence, its relevance to public health is evident. This is what epidemiological research has sought to achieve in the field of exposure to minerals examined in this book. But the epidemiological approach has its dangers and before constructing a hypothesis, it should be remembered that the strength of any association, consistency of results in different studies and consistent experimental evidence are the most powerful discriminants in examining links. Experimental work must be constructed around a hypothesis of action that is clearly defined for it to be capable of translation between species, say.

This book is a comprehensive survey of a major health concern (carcinogenesis) relating to the use of minerals. It considers all those elements about which human health concerns have been thought to exist, having defined a view of carcinogenicity that is internationally adopted in regulatory circles and which is clearly set out in initial chapters.

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Preface

Metals have played a decisive role in the development of human civilisations from earliest times. They have shaped developments in engineering, science and medicine and in the past century many Nobel Laureates were founded on research using metals. Marie Curie focussed her early research on the magnetic properties of steel but was later to perform fundamental research into the radioactivity of metals and the properties of uranium. Paul Ehrlich made notable contributions to the understanding of cancer and introduced the arsenic-related therapy Salvarsan as one of the first effective cures for syphilis and other infections prevalent at the time. Countless other memorable contributions could be included, but whilst we accept the value of metals and metalloid elements in industry and medicine, since the 1950s at least, clinicians, environmentalists and toxicologists have become aware that few substances in daily use or to which humans are exposed in daily life or in occupational environments and in medicine are entirely safe, and that a modicum of risk arises through excessive exposure, abuse or accident.

The present review re-evaluates epidemiological and occupational health studies, experimental studies in animals and *in vitro* experiments relating to the toxicity of metal and metalloid elements for which evidence of carcinogenicity has been presented. Human carcinogenic risk is substantiated in relation to arsenic, beryllium, thorium, chromium, radioactive elements, probably lead, and some nickel and cobalt compounds, and respirable silica particles, but the carcinogenicity of iron, aluminium, titanium, tungsten, antimony, bismuth, mercury, *cis*-platin, precious metals, and certain related compounds in humans is unresolved. The toxicity and carcinogenicity of each element is specific but correlates poorly with its position in the Periodic Table. Carcinogenicity differs according to the valency of the ion and its ability to interact with and penetrate membranes in target cells and to bind, denature or induce mutations by genotoxic or epigenetic mechanisms. The influence of lifestyle, environmental

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contaminants and human factors in the interpretation of epidemiological studies is discussed. Further studies are indicated to investigate the interaction between xenobiotic elements and genotype as an explanation for regional variations in population response. The relevance of experimental studies in isolation in predicting human risk through metal exposures is questioned. *In vitro* studies in mammalian cell lines and bacterial reversion tests provide evidence that certain metals and metalloid elements are capable of inducing mutagenic and clastogenic changes, but they provide limited information on target organ susceptibility, inherent protective mechanisms within the intact body or immunomodulation.

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