GENESIS OF INVESTIGATION

Life essentially is a manifestation of inorganic chemistry, according to Degens (1976). It originated from the prebiotic inorganic reactions and primitive simple covalent bond formation. The biogeochemical cycles also have made substantial contribution to the evolution of species and also to the sustenance of life on this planet. Several biological systems such as bone formation, muscle contraction, membrane phenomenon, energy production, many enzymic reactions and tissue electrolyte functions and metabolic regulations have essential dependence on inorganic processes. Application of inorganic chemistry to biological systems has gained much attention in the past three decades and a new area of studies evolved due to the success of this combination is known as Bioinorganic Chemistry. This is all the more important in the study of adverse biological effects of environmental pollutants.

Specific bioinorganic interactions are involved in the physiological response to xenobiotics (chemicals foreign to living systems) as follows:

a) comparative biochemistry of uptake, transport, target delivery, biotransformation and elimination;
(ii)

b) restricted, regulated or modified entry by membranes;
c) genetic determinants regarding growth and differentiation; and
d) defense and recovery processes.

On the basis of such effects, it may be possible to explain the diverse biological effects of different inorganic elements.

Foreign compounds such as drugs, environmental pollutants in air and water, food additives and contaminants, industrial chemicals, or cigarette smoke undergo metabolic transformations through catalysis by intracellular and extracellular enzymes. Since lung is the immediate target organ of action of inhaled xenobiotics (Rigdon, 1975; Fisher, 1976), an understanding of pulmonary biochemistry in health and disease is of paramount importance (Lensen, 1969). The health hazards due to chronic and acute inhalation of noxious substances accounts for a major proportion of occupational and environmental diseases (Hunter, 1969; Menzel, 1971). Among these, silicon containing particulates such as various forms of silica and silicates like quartz, asbestos, mica, talc, fly-ash and clay are important. Even though pathology, physiology and biochemistry of the toxic state are known, bio-inorganic processes are not fully understood. The silicate anion is implicated in toxicity. The factors deciding the chemical reactivity of silicic acid are:

a) degree of polymerization which depends on pH, concentration and presence of organic molecules;
b) hydrogen bonding with polar organic molecules;
c) silanol groups (:SiOH), and
d) ester linkages with -OH compounds.

The basic question regarding the biochemistry of Si can be understood if the process of strong binding of Si to biomolecules, both micro and macro is sufficiently known. In order to arrive at the basic chemical mechanisms of the toxic action of silicon containing dusts, the molecular interactions with proteins is studied. In terms of today's knowledge of biochemistry and cell biology, the manner in which silicon acts at cellular organelles and molecular loci is not clear due to the comparative inertness of silica in biological systems and the inherent methodological difficulties. Although the chemical mechanisms involved in the injury to respiratory systems by the dusts and organic compounds have been fairly well studied, however, in most situations, often the persons are exposed to different toxins simultaneously, which may aggravate the individual effects. The major chemical mechanisms in such effects are -

i) the qualitative and quantitative variations in the chemical reactions which the foreign substance undergoes in the presence of other xenobiotics, and
ii) direct interaction between dusts and organic chemicals.

Therefore, in the present investigation of bioinorganic mechanisms in the toxicity of dusts, chemical reactions of
organic compounds in lung tissue under normal and dust exposed
conditions is critically studied. Since the chemical processes
through which air-borne foreign chemicals get transformed in
lungs, and other aspects of the metabolic reaction of respira-
tory system are not fully understood in comparison to other
animal tissues, detailed studies were conducted in this direc-
tion also.

AIMS AND SCOPE OF THE THESIS

Aniline is the simplest aromatic amine, consisting of
one \(-\text{NH}_2\) group attached to benzene ring. It is most widely
used in industry and today one of the most important of aroma-
tic amines in the market. The danger of industrial exposure
to aniline arises from the ease with which it can be absorbed
either by inhalation or through skin. Being moderately vola-
tile, hazardous concentrations of vapour can easily arise in
industrial environment. Thus occupational and environmental
exposure to aniline vapour causes diverse toxic effects. Acute
poisoning of aniline and its homologues and by most of its
derivatives results from the inhibition of the hemoglobin
function through the formation of methaemoglobin. Asphyxia,
liver cirrhosis, and atrophy are also encountered. Therefore,
for the study of the chemical conversions of organic toxicants
in lung, aniline was selected, the metabolism of which is not
studied well. For aniline toxicity studies, the enzyme
involved in its biotransformation, i.e. aniline hydroxylase,
was dealt with in detail.
Most of the biochemical reactions transforming foreign chemicals, take place in the liver optimally. The activity of aniline hydroxylase in rat (Oppelt et al., 1970), guinea pig (Matsubara and Tochino, 1971) and rabbit lung (Bend et al., 1972) is much lower than in the corresponding livers. Despite a few reports, the catalytic role, physiological and pathological significance, and metabolic regulation of this enzyme are not known. Therefore, the defensive modulation in aniline toxicity was studied in experimental animal models. The biotransformation mechanism in lung in normal state and under stress by silica and silicate dust was studied in vitro and in vivo. These studies comprise the first part of the present study.

For this study, asbestos and quartz were selected as representatives of free silica and silicate among silica containing particulate air pollutants because these are known to be the most noxious of dusts causing asbestosis and silicosis (Birchall, 1978; Michaelis and Chissick, 1979). How such simple inert inorganic minerals cause severe biological damage is not fully known. For this, detailed understanding of the bioinorganic chemical reactions involved is needed. The basic mechanism of silica action on biological macromolecules especially protein is not understood, even though considerable evidence points out to that. Also, the basic effects of toxicity are known but the chemical mechanism by which silica influences is unknown. Therefore, silica-protein
interaction is studied in the second phase of this investigation.

In view of the above, the thesis is divided into two parts. The characterisation of the chemical mechanisms which foreign substances undergo in lung particularly organic air pollutants and how they affect in dust toxicity, along with the review of relevant literature and methodologies come in Chapter 1. Bioinorganic chemistry of silica is reviewed in health and disease and the results on silica-protein interaction presented in Part II. In the general discussion and conclusion section, the overall bioinorganic process in dust toxicity is critically appraised in the light of the findings of this author.