

SECTION III

METABOLISM AND KINETICS OF TOXIC CHEMICALS II. MECHANISMS OF TOXICITY AND THE EXTRAPOLATION OF ANIMAL TOXICITY DATA TO MAN

by
D.V. Parke

The use of laboratory animal toxicity studies in the scientific assessment of risk associated with human exposure to chemicals depends on a realistic extrapolation of this data to humans. Species differences, both qualitative and quantitative, in the metabolism and kinetics of disposition of environmental chemicals and in the sensitivity and response of receptors, are well known. In the field of therapeutics, various empirical formulae to equate various species to humans are widely used to allow for these species differences. For example, mice are frequently assumed to be some ten times less responsive, and rats some five times less responsive, to the same dose of a drug given on the weight/bodyweight basis than are human subjects. The scientific basis for this empiricism of species differences in pharmacological and toxicological response and its extension to embrace those chemicals which are metabolized to more toxic metabolites (reactive intermediates) are now discussed.

Reactive Intermediates

Although many environmental and industrial chemicals are toxic per se and are often metabolized to less toxic metabolites (detoxification), particularly where carcinogenicity and mutagenicity result, the chemicals are first metabolized to reactive intermediates. These intermediates then interact with tissue components with the initiation of toxic reactions. These reactive intermediates are highly reactive chemical species, generally electrophiles such as carbonium ions, carbenes and free radicals, which readily react with various tissue components and may become covalently bound to protein, RNA or DNA.

Simultaneous with the processes of metabolic activation, toxic chemicals also undergo the more usual metabolic detoxification. If the concentration of the environmental chemical is not so high as to overload and damage the protective chemical defence system, the major pathways of metabolism will generally be those of detoxification.