IN THE EXAMPLE OF TOXIC HEPATITIS, THE EFFECT OF CERTAIN BIOLOGICALLY ACTIVE COUCHIMCHES ON THE METABOLISM OF SUBSTANCES AND ENERGY IS STRIKING

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ANNOTATION

The article on particular topics. However, the scarcity of textbooks designed for teacher and student to use in the classroom setting that impelled us to produce the first and second editions of this work is still apparent.

With the retirement of Dr. Levi, a mainstay of the first two editions, and the continuing expansion of the subject matter, it seemed appropriate to invite others to contribute their expertise to the third edition. All of the authors are, or have been, involved in teaching a course in general toxicology at North Carolina State University and thus have insights into the actual teaching process as well as the subject matter of their areas of specialization. At North Carolina State University, we continue to teach a course in general toxicology that is open to graduate students and undergraduate upperclassmen. In addition, in collaboration with Toxicology Communications, Inc., of Raleigh, North Carolina, we present an accelerated short course at the same level. Our experience leads us to believe that this text is suitable, in the junior or senior year, for undergraduate students with some background in chemistry, biochemistry, and animal physiology. For graduate students it is intended to lay the foundation for subsequent specialized courses in toxicology, such as those in biochemical and molecular toxicology, environmental toxicology, chemical carcinogenesis, and risk assessment. We share the view that an introductory text must present all of the necessary fundamental information to fulfill this purpose, but in as uncomplicated a manner as possible. To enhance readability, references have been omitted from the text, although further reading is recommended at the end of each chapter. Clearly, the amount of material, and the detail with which some of it is presented, is more than is needed for the average general toxicology course. This, however, will permit each instructor to select and emphasize those areas that they feel need particular emphasis. The obvious

biochemical bias of some chapters is not accidental, rather it is based on the philosophy that progress in toxicology continues to depend on further understanding of the fundamental basis of toxic action at the cellular and molecular levels. The depth of coverage of each topic represents that chapter author's judgment of the amount of material appropriate to the beginning level as compared to that appropriate to a more advanced course. Thanks to all of the authors and to the students and faculty of the Department of Environmental and Molecular Toxicology at North Carolina State University and to Carolyn McNeill for much word processing. Particular thanks to Bob Esposito of John Wiley and Sons, not least for his patience with missed deadlines and subsequent excuses.

Toxicology can be defined as that branch of science that deals with poisons, and a poison can be defined as any substance that causes a harmful effect when administered, either by accident or design, to a living organism. By convention, toxicology also includes the study of harmful effects caused by physical phenomena, such as radiation of various kinds and noise. In practice, however, many complications exist beyond these simple definitions, both in bringing more precise meaning to what constitutes a poison and to the measurement of toxic effects. Broader definitions of toxicology, such as "the study of the detection, occurrence, properties, effects, and regulation of toxic substances," although more descriptive, do not resolve the difficulties. Toxicity itself can rarely, if ever, be defined as a single molecular event but is, rather, a cascade of events starting with exposure, proceeding through distribution and metabolism, and ending with interaction with cellular macromolecules (usually DNA or protein) and the expression of a toxic end point. This sequence may be mitigated by excretion and repair. It is to the complications, and to the science behind them and their resolution, that this textbook is dedicated, particularly to the how and why certain substances cause disruptions in biologic systems that result in toxic effects. Taken together, these difficulties and their resolution circumscribe the perimeter of the science of toxicology. The study of toxicology serves society in many ways, not only to protect humans and the environment from the deleterious effects of

toxicants but also to facilitate the development of more selective toxicants such as anticancer and other clinical drugs and pesticides. Poison is a quantitative concept, almost any substance being harmful at some doses but, at the same time, being without harmful effect at some lower dose. Between these two limits there is a range of possible effects, from subtle long-term chronic toxicity to immediate lethality. Vinyl chloride may be taken as an example. It is a potent hepatotoxicant at high doses, a carcinogen with a long latent period at lower.

Clinical drugs are even more poignant examples because, although therapeutic and highly beneficial at some doses, they are not without deleterious side effects and may be lethal at higher doses. Aspirin (acetylsalicylic acid), for example, is a relatively safe drug at recommended doses and is taken by millions of people worldwide. At the same time, chronic use can cause deleterious effects on the gastric mucosa, and it is fatal at a dose of about 0.2 to 0.5 g/kg. Approximately 15% of reported accidental deaths from poisoning in children result from ingestion of salicylates, particularly aspirin. The importance of dose is well illustrated by metals that are essential in the diet but are toxic at higher doses. Thus iron, copper, magnesium, cobalt, manganese, and zinc can be present in the diet at too low a level (deficiency), at an appropriate level (maintenance), or at too high a level (toxic). The question of dose-response relationships is fundamental to toxicology (see Section 1.2). The definition of a poison, or toxicant, also involves a qualitative biological aspect because a compound, toxic to one species or genetic strain, may be relatively harmless to another. For example, carbon tetrachloride, a potent hepatotoxicant in many species, is relatively harmless to the chicken. Certain strains of rabbit can eat Belladonna with impunity while others cannot. Compounds may be toxic under some circumstances but not others or, perhaps, toxic in combination with another compound but nontoxic alone. The methylenedioxyphenyl insecticide synergists, such as piperonyl butoxide, are of low toxicity to both insects and mammals when administered alone but are, by virtue of their ability to inhibit xenobiotic-metabolizing enzymes, capable of causing dramatic increases in the toxicity of other compounds. The measurement

of toxicity is also complex. Toxicity may be acute or chronic, and may vary from one organ to another as well as with age, genetics, gender, diet, physiological condition, or the health status of the organism. As opposed to experimental animals, which are highly inbred, genetic variation is a most important factor in human toxicity since the human population is highly outbred and shows extensive genetic variation. Even the simplest measure of toxicity, the LD50 (the dose required to kill 50% of a population under stated conditions) is highly dependent on the extent to which the above variables are controlled. LD50 values, as a result, vary markedly from one laboratory to another. Exposure of humans and other organisms to toxicants may result from many activities: intentional ingestion, occupational exposure, environmental exposure, as well as accidental and intentional (suicidal or homicidal) poisoning. The toxicity of a particular compound may vary with the portal of entry into the body, whether through the alimentary canal, the lungs, or the skin. Experimental methods of administration such as injection may also give highly variable results; thus the toxicity from intravenous (IV), intraperitoneal (IP), intramuscular (IM), or subcutaneous (SC) injection of a given compound may be quite different. Toxicity may vary as much as tenfold with the route of administration. Following exposure there are multiple possible routes of metabolism, both detoxifying and activating, and multiple possible toxic endpoints.

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