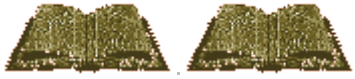
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Book Reviews: Technical Books Section



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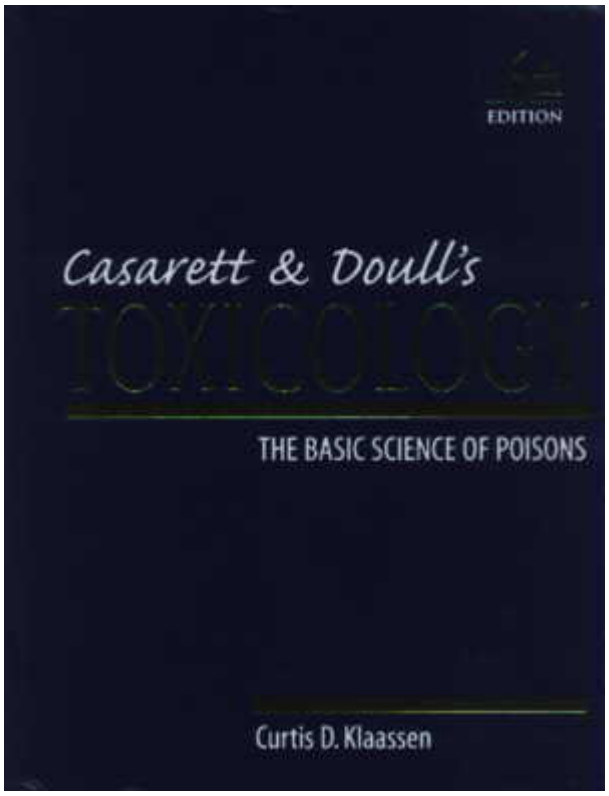
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THE ULTIMATE AUTHORITY IN TOXICOLOGY

Casarett & Doull's Toxicology - The Basic Science of Poisons, 6th Edition, *Edited by* Curtis D. Klaassen, Ph.D. Hard Bound, 8.5" x 11".
McGraw-Hill, Medical Publishing Division, Two Penn Plaza, New York, NY 10121-2298, , . Publication Date July 20, 2001. 1275 pages, ISBN 0-07-134721-6. Price $65.00

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Dr. Mary Amdur



This book has been dedicated to Dr. Mary Amdur, who was a coeditor on editions two through four. She was a distinguished toxicologist in the area of air pollution. Her work had a major role in the establishment of national and international air pollution standards. Those who worked with her remember her not only for her scientific accomplishments, but also for her wit, demeanor, and absolute honesty. The current editor Klaassen has rightly dedicated this edition to her.

Let me start with a few questions. What is toxicogenomics? What is common between WinNonlin, PKAnalyst, Summit and SAS? Which carcinogenic chemical was used in Japan from 1950 to 1975 as a cosolvent for dissolving water-insoluble analgesic drugs. Which was the first chemical discovered by man to be able to induce mutations? What special role does intraocular melanin play in ocular toxicology? What do you understand by the term Kerma? Which is the only late effect of ingestion of ^{226,228}Ra? In 1884, cases of "hepatitis" were found in cattle in Iowa. What was the cause of this hepatitis?

If you want to find out the answers to these and millions of other similar questions on toxicology, then this book is for you. The first edition of Casarett and Doull's Toxicology came out more than a quarter century before - in 1975, and since then this book has become somewhat of a classic. When initially launched it was intended not only as a text for toxicology students but for as wide a variety of audience as research scientists and those concerned with community health, agriculture, food technology, pharmacy and even veterinary medicine. That edition was divided in four units. Over time Casarett and Doull has grown enormously. The present edition has seven units. The basic audience remains as wide and diversified as it was for the first edition.

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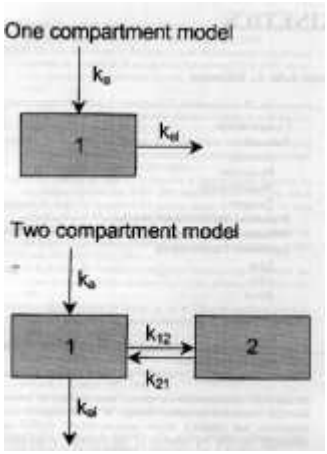
Unit 1 discusses the general principles of toxicology. Topics such as history and scope of toxicology and general principles of toxicology are discussed in this unit. History of toxicology is dealt with from the ancient era till modern times, when ecological disasters such as the Love Canal disaster led to a great deal of legislations. Just for recapitulation, Love Canal does not get its name from love making couples on its banks, but from the name of William T. Love, who in 1892, proposed digging a canal to connect the upper and lower parts of the Niagara River. The plan was to connect Lake Ontario and Lake Erie bypassing Niagara Falls in order to serve as a water power conduit.

...The professional activities of toxicologists fall into three main categories: mechanistic, descriptive, and regulatory. What are these? Well, the book goes on to describe each of them in great detail...

The canal was never completed but the Hooker Chemical Company, located west of the canal, had the ingenious idea of turning the uncompleted canal into a dumping ground for the chemical by-products of its manufacturing process. Once the canal was filled with waste, the land was covered over and sold to the Niagara Falls city school board for $1.00 and a school and subdivision of homes was built right on top of the waste. Much later it was found that these chemicals were slowly leaking. Residents living in these areas were found to have abnormal chromosomal damages. The area surrounding the Canal was vacated and very soon it turned into a ghost town. Historical instances such as these teach us to be vigilant in the future.

What are the different areas of toxicology? Chapter 2 entitled "Principles of Toxicology" enlightens us on that. The professional activities of toxicologists fall into three main categories: mechanistic, descriptive, and regulatory. A mechanistic toxicologist is concerned with identifying and understanding the cellular, biochemical and molecular mechanisms by which chemicals exert toxic effects on living organisms. A descriptive toxicologist is concerned directly with toxicity testing, which provides information for safety evaluation and regulatory requirements. A regulatory toxicologist has the responsibility for deciding, on the basis of data provided by descriptive and mechanistic toxicologists, whether a drug or another chemical poses a sufficiently low risk to be marketed for a stated purpose. The unit goes on to discuss subjects like classification of toxic agents, characteristics of exposure, spectrum of undesired effects and so on.

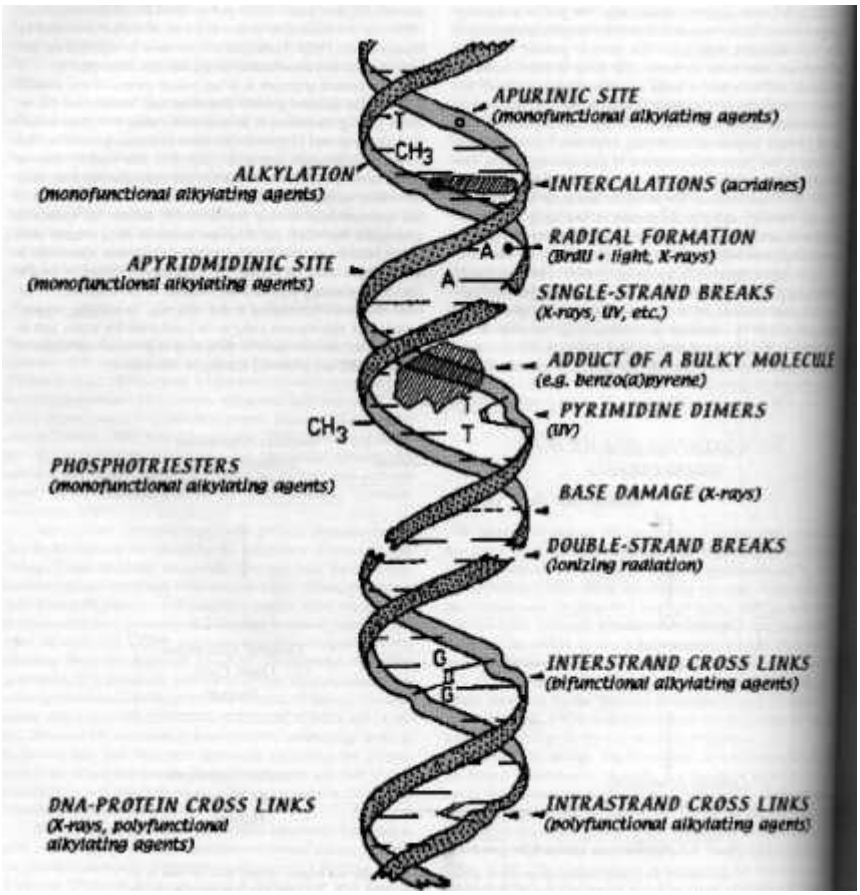
Compartmental pharmacokinetic models. This diagram appearing on page 226 explains the concept of one-compartment and two-compartment models.



Unit II discusses about the disposition of toxicants or how are they disposed off. This unit has chapters on absorption, distribution and excretion of toxicants, biotransformation of xenobiotics and toxicokinetics. I am particularly interested in toxicokinetics and I straightaway moved on to that, how that topic was dealt with. And I found this chapter very informative. It tells us about the one-compartment model, and the two-compartment models. A one-compartment model refers to the body as a single compartment. Compounds which mix uniformly or which equilibrate rapidly can be described with a one-compartment model. The one compartment model depicts the body as a homogenous unit; there is no difference between blood and tissues as far as distribution of drug is concerned. Its concentration remains the same everywhere. Not every compound however can be described by the one-compartment model. There are many which take time to equilibrate; so much so that the blood and tissue concentrations can differ substantially. These compound are best described by the two compartment model.

Unit III deals with non-organ-directed toxicity. This reviewer found this unit particularly interesting and useful, especially as routine textbooks hardly devote much space to this aspect of toxicology. In this unit you get to read such topics as chemical carcinogenesis, genetic toxicology and developmental toxicology. I turned to Genetic Toxicology in this unit, as it is such a new discipline, and not much has been written about it. Many toxicologists find it hard to differentiate between genotoxicity and mutagenicity. The author explains the differences at the outset. Matagenicity is a much restricted phenomenon. It refers to genetic events, which are transmissible from cell to cell and from generation to generation. Genotoxicity on the other hand is a much broader term; it includes not only mutagenicity but also such events as unscheduled DNA synthesis, sister chromatid exchanges, and DNA strand breaks, which are not transmissible. The author goes on to give a very interesting history of genetic toxicology and then explains the major concepts. An explanatory diagram on page 326 serves to clarify several concepts.

Spectrum of DNA damage induced by physical and chemical agents. This diagram appears on page 326 and clarifies many concepts relating to genetic toxicology.



Unit IV deals with target organ toxicity. This is another area which is not dealt with in any detail in routine text books. This unit deals with how various body organs respond to poisons. There are chapters on Toxic responses of the blood, immune system, liver, kidney, respiratory system, nervous system, ocular and visual system, heart and vascular system, skin, reproductive system and the endocrine system.

Unit V deals with individual toxic agents such as pesticides, metals, solvents and vapors, radioactive materials, and poisonous animals and plants.

Unit VI deals with environmental toxicology. It has chapters on air pollution and ecotoxicology. The term ecotoxicology was introduced by Truhaut in 1969. It is best defined as the study of the fate and effects of toxic substances on an ecosystem and is based on scientific research employing both field and laboratory methods.

Unit VII, the last unit in the book, deals with applications of toxicology. It has chapters on food toxicology, forensic toxicology, clinical toxicology, occupational toxicology and regulatory toxicology. Being a forensic toxicologist, I was particularly interested in reading the chapter on forensic toxicology. Written by Alphonse Poklis, Professor of Pathology at the Virginia Commonwealth University, it gives analytical techniques and their interpretation. There are sections on Criminal Poisoning in the Living, Forensic Urine Drug testing, Human performance testing, Courtroom testimony, Analytical role in clinical toxicology, therapeutic monitoring and biological monitoring.

As you open the book, you at once begin to get influenced by its visual appeal. The text in black interspersed with blue headings and sub-headings appears very refreshing. Several titles and subtitles are very "catchy". Sample this: On page 219 you see a subtitle saying - "Phosphorylation -

The Dog That Did Not Bark". This is a chapter on *Biotransformation of Xenobiotics* (Chapter 6), and the author is talking about Phase I and Phase II reactions. Just for recapitulation, all xenobiotics (drugs, chemicals, poisons) are metabolized in the body by Phase I and Phase II reactions. Phase I reactions generally involve oxidation, reduction and hydrolysis of compounds. These reactions expose or introduce a functional group such as -OH, -NH_2, -SH or -COOH. They generally result in the loss of pharmacological activity and a very small increase in the hydrophilicity of xenobiotics. Phase II reactions are conjugation reactions, in which a covalent link is formed between the functional group on the parent compound or Phase I metabolite with endogenously derived glucuronic acid, sulfate, glutathione, amino acids or acetate. These highly polar conjugates are generally inactive and are rapidly excreted in urine and feces.

QUICK NOTES

Some major highlights of *Casarett & Doull's Toxicology* at a glance:

- Comprehensive coverage
- New areas such as genetic toxicology, toxic effects of radiation and radioactive materials covered in detail
- Each chapter written by a specialist in his own area of specialization
- Applied aspects of toxicology dealt with
- Target organ toxicity and non-organ-directed toxicity dealt with; this usually does not find mention in other toxicology text books.

While discussing Phase II reactions, the author tells us that these reactions are very ATP-intensive, i.e. they require a large amount of ATP molecules. This makes the reaction very inefficient. The author asks himself the question, "Why is ATP not used directly by phase II enzymes?" Or in other words, "why are xenobiotics never phosphorylated, which would require less ATP which would require less ATP and would achieve the goal of converting xenobiotics to water-soluble conjugates." Or to put it metaphorically why does the dog - the phosphorylation - does not bark here. The author goes on to give three interesting reasons, which the reader would love to read. Catchy titles and subtitles like these make the text appear very interesting.

At a number of other places, you encounter interesting quotes. Sample this one which appears on page 8: "You too can be a toxicologist in two easy lessons, each of ten years". The quote is attributed to Arnold Lehman (circa 1955). This quote appears in Chapter 1 on "History and Scope of Toxicology". A number of other interesting quotes appear off and on throughout the book. In this reviewer's opinion, they serve to make the text lighter and more interesting.

Still wondering about the answers to the questions I asked in the beginning? You would do well to read the answers in the book itself, but for those who can't wait enough here are the answers. Toxicogenomics is a futuristic subdiscipline of toxicology which enables a mechanistic toxicologist to identify and protect genetically susceptible individuals from harmful environmental exposures, and to customize drug therapies that enhance efficacy and minimize toxicity, based on their individual genetic makeup (page 12).

...I would highly recommend this book to all clinical and forensic toxicologists, researchers in toxicology, clinicians, environmental toxicologists, food toxicologists, agricultural scientists, clinical chemists, and a number of other professionals who encounter xenobiotics in their daily professional life...

WinNonlin, PKAnalyst, Summit and SAS are all computer software programs which can do compartmental modeling of pharmacokinetic data (page 230). Ethyl carbamate was used in Japan to dissolve water-insoluble analgesic drugs. This chemical is carcinogenic for many tissues in the mouse (page 244). The first chemicals found to be able to induce mutations (in *Drosophilia*) were nitrogen mustards. In 1946, Charlotte Auerbach and colleagues discovered that they could induce mutations in *Drosophilia*, and with this discovery the field of chemical mutagenesis was laid wide open (page 322). Intraocular melanin has high binding affinity for polycyclic aromatic hydrocarbons, electrophiles, calcium, and toxic heavy metals such as aluminum, iron, lead and mercury. Although this may play a protective role in the beginning, it ultimately results in excessive accumulation of these xenobiotics, long term storage and slow release of numerous drugs and chemicals from melanin. One example would make it amply clear. Lead accumulates in human retina so much that its concentration can be 5 to 750 times that in other ocular tissues (page 570).

Kerma is an acronym for Kinetic Energy Released In Matter (page 921). It is a unit which we use in connection with the toxicity of uncharged particles such as gamma rays and neutrons (this term incidentally comes from a chapter entitled "Toxic effects of radiation and radioactive materials"). The only late effect of ingestion of ^{226,228}Ra is osteogenic sarcoma (page 926). The cause of hepatitis in cattle in Iowa was ingestion of species of *Senecio* (ragwort or groundsel, aster family)

I would highly recommend this book to all clinical and forensic toxicologists, researchers in toxicology, clinicians, environmental toxicologists, food toxicologists, agricultural scientists, clinical chemists, and a number of other professionals who encounter xenobiotics in their daily professional life. And of course undergraduate and postgraduate students of toxicology would find this book immensely useful.

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