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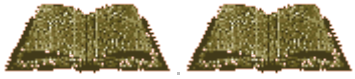

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LATEST RESEARCH IN TOXICOLOGY AND PHARMOCOLOGY

Annual Review of Pharmacology and Toxicology , Volume 41, 2001*Edited by* Arthur K. Cho (Editor), Terrence F. Blaschke (Associate Editor), Paul A. Insel (Associate Editor) and Horace H. Loh (Associate Editor)
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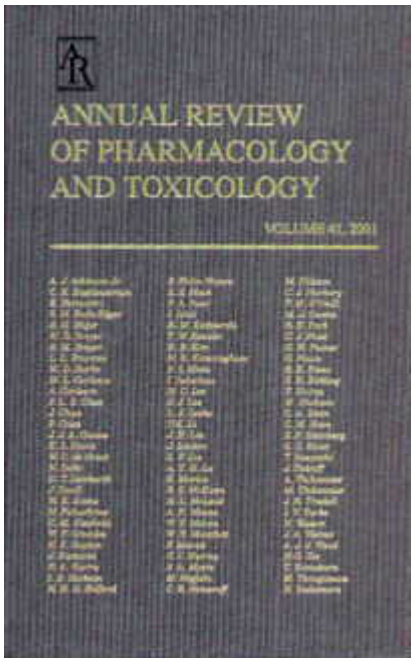


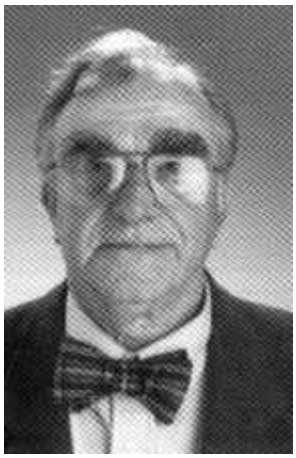
For the last almost 40 years, the Annual Review of Pharmacology and Toxicology has been giving us the gist of the latest developments in the field of pharmacology and toxicology. Each volume is a sheer pleasure to read, and the current edition is no less.

A wide range of topics covering toxicology and pharmacology are covered in this book. The book opens with a very enlightening chapter by John Doull, whom we all know as the co-editor of the very successful *Casarrett and Doull's Toxicology*, a book which has been with us for almost a quarter of a century now, and has seen as many as five editions.

In this chapter (entitled "Toxicology Comes of Age"), Doull traces the history of toxicology, especially in the 20th Century, and nostalgically remembers his own experiences in pharmacology at the University of Chicago and the University of Kansas Medical Center. Two of the key players in the development of toxicology were from the University of Chicago. These were Dr. Eugene Maxmilliam Karl Geiling and Dr. Kenneth Patrick DuBois. When these scientists were academically active, Doull was a graduate student, and fondly recounts his experiences there.

View this book on Amazon

John Doull



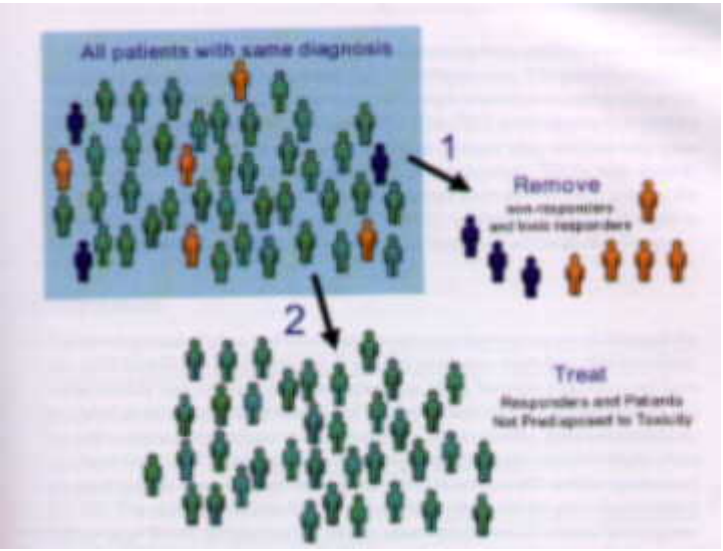
The University of Chicago Toxicity Laboratory, also known as the "Tox Lab" was created in 1941. Doull joined the lab in 1946 after receiving a BS in chemistry from Montana State College in 1944

and then spending two years in the navy. At that time, Dr. George Mangun was the director of the "Tox Lab". He suggested that he switch over to pharmacology and work with Dr. DuBois. Doull agreed to this and subsequently wrote a Ph.D. thesis on the "cardiotoxic and other effects of bufagin". Bufagin is a toxin which Doull obtained from the parotid gland of the giant toad *Bufo marinus*. For the study, this toxin had to be labeled, which he did by feeding the toads ^{14}C-labeled algae. His other areas of research were the Organophosphorus (OP) insecticides.

Doull then goes on to give accounts of various journals and textbooks, which helped to raise the study of toxicology to the level of an academic discipline. The *Journal of Toxicology and Applied Pharmacology* was started in 1959, mainly because of the reluctance of the *The Journal of Pharmacology and Experimental Therapeutics* to publish toxicology studies on products or chemicals. This was a major step in the history of toxicology according to Doull, and helped raise toxicology to the level of an academic discipline.

The *Journal of Toxicology and Applied Pharmacology* became the official journal of the Society of Toxicology in 1963, yet the Society did not own it. Its very own journal was started in 1981. This was called *Fundamental and Applied Toxicology*. The name of this journal was changed to *Toxicological Sciences* in 1998. This journal now has new sections, such as the one titled "Profiles in Toxicology", which calls attention to historical events and contributors to toxicology. Doull considers the launching of these two journals very important in the history of 20th Century Toxicology.

Rational selection of patients on the basis of Pharmacogenomics. The patients who are non-responders (yellow) and those who are toxic responders (blue) are segregated beforehand from those who are likely to respond well (green).



Doull then goes on to describe some textbooks which were written during this period. The first American book on toxicology was written in 1959 by DuBois and Geiling. In 1968 Ted Loomis came out with a second book, which saw its fourth edition in 1996 as *Loomis's Essentials of Toxicology*, with Wally Hayes as a coeditor (*Academic Press*).

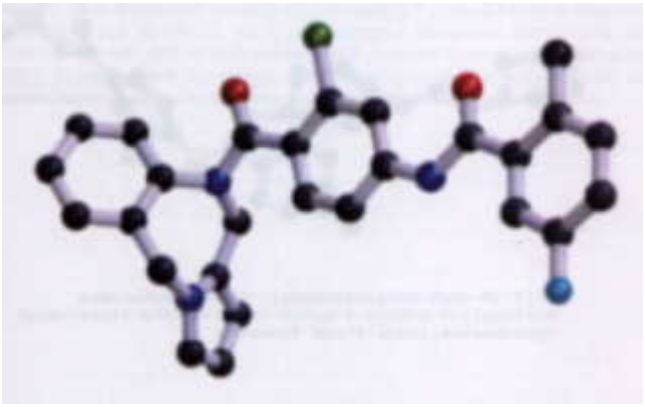
Doull then describes the evolution of his own book. In 1967 Lou Casarrett was searching for a toxicology textbook that would include both the classes of poisons (such as metals, solvents, pesticides etc) and the organ system involved (heart, lungs, kidneys etc). Since none of the existing books offered this approach he decided to write his very own textbook on these lines and roped in Doull for this work. Unfortunately Lou developed brain cancer (I was pained to learn later that in

1989 Doull himself developed kidney cancer), and much of his work fell on his wife Peggy, who would read chapters aloud to Lou and handle the correspondence with the authors. Their work was first published in 1975 as *Toxicology, the Basic Science of Poisons*. The name was later changed to *Casarrett and Doull's Toxicology* to provide a fitting memorial to Lou's dedication to toxicology.

The rest of the chapter is also very absorbing, but I would rather let the reader read the whole chapter and enjoy this very finely written history of toxicology.

OPC-31260 and VPA-985, two V_2-Renal receptor antagonists likely to be useful in liver cirrhosis and nephrotic syndrome.



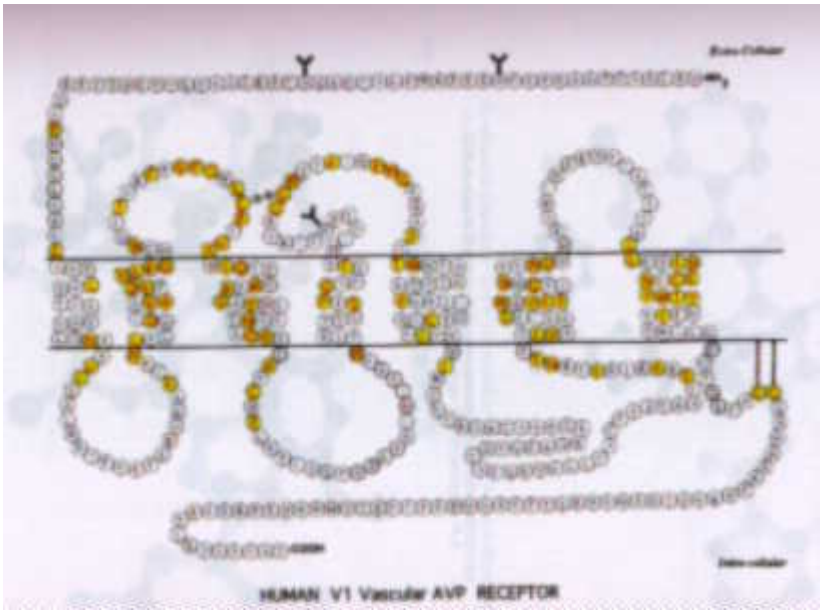


There is an interesting chapter on Pharmacogenomics by Howard L McLeod and William E Evans. This is a relatively new science which deals with unlocking the human genome for better drug therapy. There is a great variation in patients' responses to various drug therapy, and often the optimum drug for a particular patient is decided by the physician's experience. This chapter tells us that the variations in responses to drug therapy could be as a result of genetic variations. The science of Pharmacogenomics aims to predict these variations beforehand so that physicians could chose the best therapy for the patient on a more rational basis. Understanding the molecular basis of drug action and genetic determinants of drug response should enlighten the use of many medications, towards the ultimate goal of giving the right drug at the right dose to the right patient at the right time.

The authors ask us at one place," How does one rationally select the best treatment option for hypertension in a 78-year-old Caucasian female when there are nearly 100 different diuretics, beta blockers, calcium channel antagonists, angiotensin-converting enzyme inhibitors, alpha adrenergic blockers and angiotensin II receptor antagonists available?" The answer in the current scenario is that the choice is empirical if not arbitrary. By understanding the mechanisms of drug action at the molecular level, and understanding how genetic variations affect drug action, physicians ultimately hope to chose drugs for the patient more rationally and scientifically. The accompanying diagram

shows how this can be done. The blue box shows all people with the same diagnosis, but many of them are not destined to respond favorably to a particular drug. Instead of choosing the right drug for them by hit and trial (as is done currently), the inappropriate patients are segregated to begin with. These are the patients who are either going to show no response to the treatment (non-responders) or show toxicity (Toxic responders).

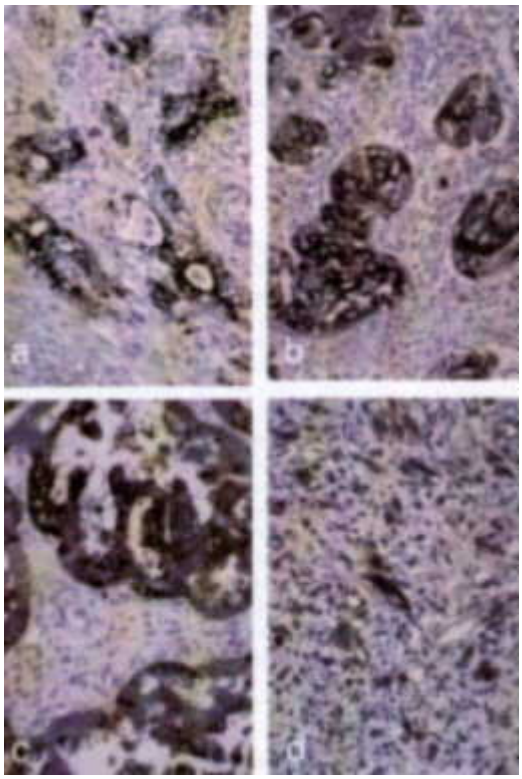
Two dimensional model of the human V_1-vascular AVP receptor.



Many chapters are there on the pharmacology and toxicology of various receptors, especially G protein-coupled membrane receptors. One chapter that particularly caught the attention of this reviewer is entitled "The Basic and Clinical Pharmacology of Nonpeptide Vasopressin Receptor Antagonists" written by M. Thibonnier and his three other colleagues. The chapter talks about the clinical uses of antagonists to the neurohypophyseal hormone Arginine VasoPressin (AVP). It is a cyclic nonpeptide whose actions are mediated by G protein-coupled membrane receptors. Three main receptors subtypes have been classified pharmacologically. These are V_1-vascular (V_1R), V_2-Renal (V_2R) and V_3-Pituitary (V_3R). Antagonists to these receptor subtypes could be clinically useful in a number of situations. Blockade of V_1-vascular would be useful in arterial hypertension and peripheral vascular disease. Blockade of V_2-renal AVP receptors would be useful in liver cirrhosis, nephrotic syndrome and any state of excessive retention of free water. Blockade of V_3-pituitary AVP receptors would be useful in the treatment of adrenocorticotropin-secreting tumors. The chapter reviews the pharmacology of these receptor antagonists.

Besides AVP, oxytocin (OT) is another neurohypophyseal peptide involved in uterine contractions and milk ejection. In fact OT receptors play a major role in parturition. If OT receptors could be blocked with specific OT receptor antagonists, an effective tocolytic treatment could be initiated, which could be helpful in premature labor and delivery. Similarly the blockade of V_1-vascular AVP receptors in the nonpregnant uterus may alleviate the symptoms of primary dysmenorrhea.

The immunohistochemical localization of CYP1B1 in individual types of human malignant tumors. The tumors are (a)stomach cancer (b) esophageal cancer (c) Ovarian cancer and (d) rhabdomyosarcoma.



Another chapter that caught this reviewer's attention is entitled "Regulation, function and tissue specific expression of cytochrome P450 CYP1B1" by Graeme I. Murray and his three other colleagues. Till fairly recently it was believed that the cytochrome P450CYP1 family consists of only one subfamily containing two very well characterized members CYP1A1 and CYP1A2. In 1994 however a new member of this family was cloned, which was designated CYP1B1. Although this compound showed just about 40 percent homology with either CYP1A1 or CYP1A2, the P450 nomenclature committee assigned this compound to a new CYP1 subfamily CYP1B. DNA hybridization studies have suggested that no new members of this new subfamily exist.

The authors go on to describe the structure of this new compound. It is the largest known human P450, being about 543 amino acids long. The associated mRNA is 5.2 kb. The related gene is located on chromosome 2p22-21 spanning approximately 12 kb of DNA and is composed of three exons and two introns. The interesting thing is that CYP1B1 is capable of metabolizing a variety of putative human carcinogens. It is also expressed in a variety of human tumors. Thus CYP1B1 is a very good tumor biomarker. It is also inducible by dioxin (in fact the group that discovered it in 1994 cloned it from a keratinocyte cell line that had previously been treated with tetrachloro-dibenzo-p-dioxin). This fact is relevant to toxicologists.

Other chapters relate to such topics as the novel effects of nitric oxide, role of adenylyl cyclase isoforms, biological activities of thioredoxins, subtypes and signaling of prostanoid receptors and molecular targets of lithium action. This is really a very comprehensive guide to latest pharmacological and toxicological research occurring in the last two or three years. Fully recommended for all toxicologists, pharmacologists, and all medical personnel who have a role in the treatment of patients.

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