Five years away

A well accepted axiom of medicine is that there is no such thing as a completely safe drug. Even aspirin has its problems, inducing bleeding in the stomach lining. More potent agents can produce more serious side effects, including damage to liver, kidney and bone marrow cells.

Says Dr. Elliot S. Vesell, "One of the central problems of clinical pharmacology is the alarmingly high incidence of drug toxicity." By this, Dr. Vesell, who is chairman of pharmacology at the Milton Hershey Medical Center in Hershey, Pa., refers to adverse reactions from small or moderate doses of drugs. Toxicity from overdosing is a separate issue.

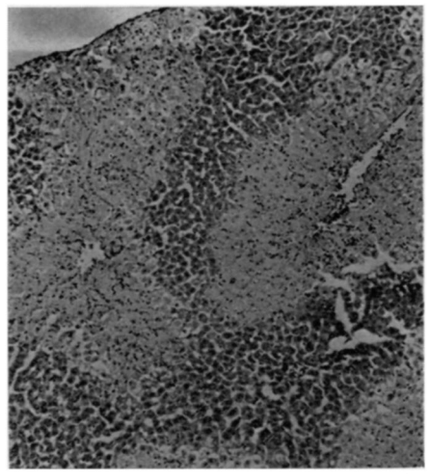
Drug toxicity was among the primary questions discussed last week in New York at a conference on Drug Metabolism in Man, sponsored by the New York Academy of Sciences. In zeroing in on the problem, researchers presented data showing that the same drug, given in different ways, may be handled in separate ways by the body; that one drug may interact with another, thereby altering the metabolic fate of both—a survey of patients at Johns Hopkins showed that the average patient is taking as many as 15 drugs at once during his hospital stay—and that the best indication of drug activity is derived by measuring its level in blood plasma (see p. 37).

Conference participants agreed that careful and frequent analysis of plasma levels is essential to good medical practice. They conceded that few laboratories are presently equipped to measure plasma levels routinely and that new, simpler techniques are required. A few new tests were reported at the conference.

While more sophisticated practice may be the best immediate solution to the hazards of drugs, the design of nontoxic compounds, agents that produce only the desired effect without causing adverse reactions, is the ideal answer. On the basis of experiments conducted within the last six months that have yielded a new theory of the mechanism of drug toxicity, Dr. Bernard B. Brodie predicts that it may be possible to create nontoxic drugs within three to five years. Dr. Vesell calls Dr. Brodie's theory "one of the most exciting new approaches to toxicity."

Dr. Brodie and his colleagues at the National Heart and Lung Institute, including Drs. James R. Gillette, A. K. Cho, G. Krishna and W. D. Reid, are probing drug toxicity at the molecular level.

The scientists were seeking an explanation to the fact that many therapeutic agents, relatively inactive chemically, are able, in some patients, to produce tissue lesions. They formulated a hypothesis: In order for a drug to produce a tissue lesion it must cause cellular damage by forming covalent bonds with various cell components, either directly or through metabolites. Preliminary experiments support their idea.



Dr. Brodie

Massive liver damage from epoxides.

It all began in Australia where Dr. Brodie was traveling, mainly to see various kinds of marsupials. "After my interest in kangaroos and koala bears was exhausted," he recounts, "I visited a sheep station, a name given to a vast expanse of inhospitable territory containing 100,000 or more sheep. There, I became aware of a problem of some concern to sheep ranchers."

It seems that sheep are dewormed by administration of generally nontoxic doses of carbon tetrachloride. Occasionally, however, a group of sheep succumb to the drug, showing massive liver-cell damage at autopsy. "I was well aware," Dr. Brodie says, "of the toxic effects of carbon tet on the liver and kidney, but for the first time it struck me that CCl_4 is an exceedingly inert compound in the test tube, reacting with other chemicals only under rather extreme conditions." Then, in Brisbane, he met a pathologist who had discovered that pretreating sheep with phenobarbital dramatically enhances the toxicity of carbon tet, leading in virtually all cases to massive liver damage from otherwise nontoxic doses. Phenobarbital markedly stimulates the activity of drug-metabolizing enzymes in the liver.

This, Dr. Brodie recalls, led to another thought. "I remembered that a considerable number of compounds, especially halogenated hydrocarbons used as industrial solvents, were even more chemically inert than carbon tet, but were also relatively specific in producing liver and kidney necrosis."

Putting these thoughts together, Dr. Brodie and his colleagues came up with the hypothesis to account for tissue lesions and tested it by studying halogenated hydrocarbons and carbon tet. Disclosure of the toxic mechanism of these relatively inactive compounds, they reasoned, would lead to insights into tissue lesions caused by therapeutic drugs. In essence, they found that these compounds undergo a somewhat unusual metabolic transformation, being converted by the liver to moderately stable epoxides, alkylating agents which destroy the very cells that produce them.

A liver enzyme, cytochrome P-450, captures oxygen from the atmosphere so that it can react directly with various substrates. Normally, it converts those substances with which it reacts to epoxides. The epoxides are highly unstable. In the presence of proteins in tissue they are immediately molecularly rearranged to form harmless compounds called phenols.

However, the stability of various epoxides varies. In the case of halogenated hydrocarbons and carbon tet, the epoxides formed in the presence of liver enzymes are just stable enough to react covalently with proteins or nucleic acids, thereby creating the type of molecular bond that destroys the cell.

With this knowledge, it is possible to consider ways of altering a compound to prevent its metabolism to a moderately stable, and lethal, epoxide. In this way research moves into structure-function relationships. Knowing what molecular structures form epoxides or alkylating agents, scientists should be able to modify the structure of a compound sufficiently to block that formation without disturbing the molecular architecture so much that therapeutic activity of drugs is lost. "Except for antimetabolites and antibiotics," Dr. Brodie declares, "most drugs act directly at specific receptor sites and the toxicity resulting from certain metabolites is unrelated to therapeutic action." □

INCH BY INCH

East-West physics

International collaboration in the conduct of experiments is now customary among high-energy particle physicists. The world contains only a few of the large accelerators needed to do the work, and international collaboration gives physicists of all nations a chance at them.

With most nations such collaboration is fairly easy to arrange. But when the Soviet Union is a partner, complicated diplomatic maneuvering becomes neces-