

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 thera-



Dr. Brodie

Massive liver damage from epoxides.

peutic 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.

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 CCl₄ 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-

sary, because the Soviets demand detailed written agreements to cover all contingencies. Yet Russia possesses the world's largest particle accelerator, the 76-billion-electron-volt (GeV) proton accelerator at Serpukhov, near Moscow. So in spite of all difficulties, Western interests persist in negotiating with them.

So far agreements have been concluded giving access to Serpukhov scientists from France and from the European international laboratory, CERN. American physicists would also like to work at Serpukhov, and it now appears that a group of them may have the opportunity, even though negotiations with the Soviet Government on a protocol covering American admission to Serpukhov is stalled on Russian insistence on getting hardware as an admission fee.

A group of physicists from the University of California at Los Angeles, led by Dr. Darrell Drickey, has been invited to participate in an experiment to probe the structure of the pi meson by the East European international laboratory, the Joint Institute for Nuclear Research at Dubna in the U.S.S.R. The work will be done at Serpukhov, and an invitation from the Serpukhov management as well as final political approval is still necessary.

Since the experiment is scheduled to start on Oct. 15, the Americans urged that the joint project be permitted to go forward on some unofficial basis. A letter from Dr. Andronik M. Petyants, chairman of the Soviet State Committee, to Dr. Glenn T. Seaborg, Chairman of the U.S. Atomic Energy Commission, now suggests that the experiment can go through.

The experiment will collide electrons and pi mesons in an attempt to find out something about the structure of the pi meson: whether it is the same size as the proton or not. The pi meson plays a key role in current theories of the structure of neutrons and protons and of the strong force that binds them together.

To cover the legalities of the UCLA-Dubna-Serpukhov collaboration, a protocol that both sides have already accepted is suggested. It allows directors of laboratories in either country to invite scientists from the other country to participate in research. It is different from the still-disputed protocol that would give Americans access to Serpukhov under special conditions. A formal invitation from the management of Serpukhov to the UCLA group to come and participate in the experiment is awaited.

Under the same invitation protocol another American, Dr. Zaven Guiragossian, wants to participate in a Serpukhov experiment. He has been invited by the Yerevan Physics Institute in Armenia to collaborate with some

Yerevan staff members who will work at Serpukhov. To go he needs a grant. His application is under active consideration at the AEC, says Dr. William A. Wallenmeyer, assistant director for high-energy physics programs, but no decision has been made.

Meanwhile two scientists from Serpukhov are at the National Accelerator Laboratory in Batavia, Ill. They are participating in discussions among prospective users of the 200-400 GeV accelerator under construction there to see what use Russian physicists might make of it.

Access to Batavia was what the Americans offered the Russians in return for American access to Serpukhov, but the Russians insisted on getting hardware as well, and the Americans refused. Now, says Dr. Wallenmeyer, there are signs that the Russians may be getting ready to drop the insistence on hardware, though they haven't said so officially yet. □

OPINION SURVEYS

Asking the right questions

"Would the fact that Governor Rockefeller has not denounced President Nixon's Indochina policy be a reason for you not to vote for him in November?" This question, in the form of an art exhibit, confronts visitors at the "Information" exhibition that opened last week at New York's Museum of Modern Art. The visitor has the opportunity to respond to artist Hans Haacke's exhibit with "Yes" or "No" ballots that are dropped into a transparent box. So far the voting has been loaded in the "Yes" direction.

Haacke's exhibit serves both to convey information to the potential November voter—Rockefeller's support of Indochina policies—and to shape the direction that the voter will cast his ballot: against Rockefeller.

The use of questions and questionnaires to convey information and to shape political opinion dates back at least to the Goldwater Presidential campaign of 1964. "The Goldwater forces used opinion surveys only partially for polling purposes," says Dr. Dan Nimmo, author of *The Political Persuaders*. "They were primarily interested in influencing people to recognize Goldwaters' name and political positions. And of course to affect a favorable response to the candidate.

"In fact," he says, "this technique suggested to a number of political consultants that questionnaires were not actually for polling information but rather for influencing voting behavior." The results of such surveys are rarely published, or when they are, it is only to influence potential voters further.

The biased questionnaire as an instru-

ment of opinion change has been of recent research interest to Drs. Ronald Dillehay of the University of Kentucky and Larry Jernigan of Texas Christian University. They designed questionnaires that were systematically biased so that subjects would respond in the manner that the researchers desired. "We want to put words in the subject's mouth, so to speak," says Dr. Dillehay. "Then we investigate any subsequent changes in opinions."

The researchers developed three parallel questionnaires concerned with the treatment of criminals. One questionnaire favored harsh treatment, another favored lenient treatment and the third had no systematic bias. In order to produce bias they used highly suggestive words at the beginning of sentences, such as "wouldn't," "isn't"; stereotypes, such as "hardened criminals"; response alternatives phrased so that the desired response was logical, the undesired response illogical or absurd.

Each of the biased questionnaires was administered to 30 persons. Fully 86 percent of the responses to the lenient questionnaire were in the direction desired; 67 percent of the responses to the harsh questionnaire were in the direction designed.

After the subjects had completed the experimental questionnaire, they were polled with another set of measures regarding their attitudes toward criminal treatment. Subjects who were exposed to the lenient questionnaire favored lenient punishment on the independent measures. But the subjects who were exposed to the harsh questionnaire did not differ in their attitudes toward punishment from those who had been exposed to the neutral questionnaire.

In a post-experimental assessment only a third of the subjects reported that they thought the questionnaires were biased. Perhaps this is the most surprising finding. "We have tested some very sophisticated people," says Dr. Dillehay, "and they are by and large taken in by this process. To say the least, it is highly undesirable."

The questionnaires that Congressmen send out to potential voters and constituents are often less to assess political opinion than to shape it. These questionnaires are part of the parcel of the sophisticated techniques of communication and persuasion that are increasingly being applied to affect the political process, according to campaign managers who develop and use the technique.

"Unfortunately, anyone can crank out surveys and opinion questionnaires at present," says Hank Parkinson, a consultant based in Wichita, Kan. "The result is that polling of this type often unfairly influences elections. Eventually this inaccurate type of polling will have to be outlawed." □