HOW GENES CONTROL DRUGS

Evidence suggests that genetic factors determine individual drug reactions. The study of these genetically triggered responses shows clinical promise.

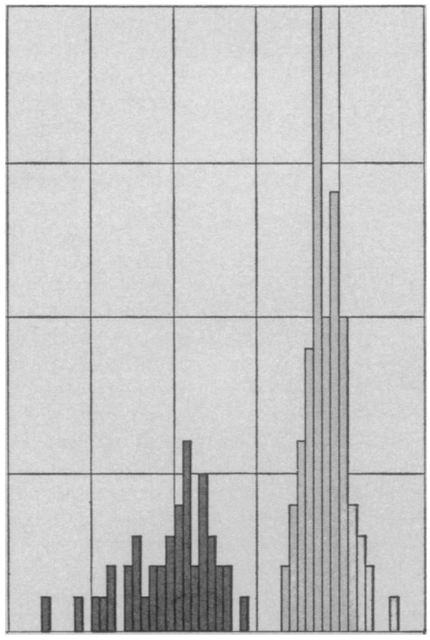
by Joan Lynn Arehart

Even in this age of space flight and nuclear medicine, the physician's main criterion for deciding drug dosage is still what it has been for the past half century—a patient's weight. Nor are the physician's guidelines for selecting a medication that much more sophisticated. He can check the Physician's Desk Reference, hark back to his pharmacology textbook from his second year in medical school or dredge up past clinical experience he and his colleagues have had with the drug. That's pretty much all there is to drug prescribing, or all there has been—until recently.

Quietly, low-key but definitively, pharmacology is moving from cursory description to finely honed measurement of bodily drug events—much as the entire field of biology has turned during the past century from description to measurement to alteration of biological reactions. A major advance pharmacologists are now serving up to physicians has to do with "pharmacogenetics," the study of genetically triggered individual responses to drugs. More and more clinicians are tuning in to pharmacogenetics. It should help them prescribe more rationally.

Calling on pedigree studies, pharmacology-toxicology assays and the latest biochemical techniques, pharmacogeneticists are coming up with some exciting results. For one, there is definite proof that some adverse drug reactions can be inherited (SN: 11/30/68, p. 551). Pedigree studies have shown that certain adverse drug reactions run in families. Dose response curves reveal astonishing variations in individual responses to drugs.

For example, Drs. Elliot S. Vesell and John G. Page, originally working at the National Institutes of Health, have observed that blatant individual variations in response to drugs vanish in identical twins but remain largely preserved in fraternal twins. The drugs they studied included ethanol, dicumarol (an anticoagulant), halothane (an anesthetic), phenylbutazone (for arthritis) and antipyrine (for headaches). The studies were designed to assure large environmental differences and living habits. The results showed that large individual differences in the rates at which the subjects metabolized drugs were influenced negligibly by environmental factors; the rates were under complete genetic control.



Hospital Practice

Drug-response distribution curve. Two genetic populations apparent.

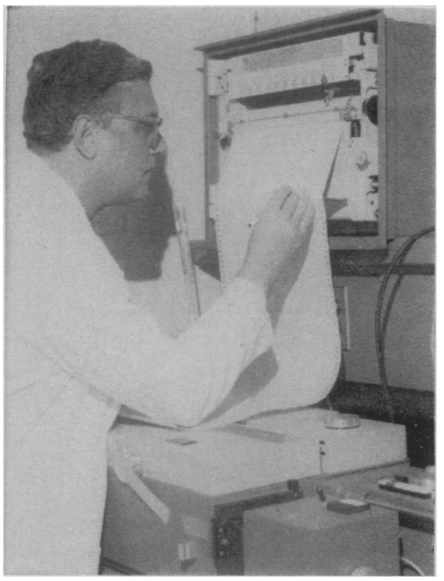
There is also evidence that people show patterns of responses to a gamut of drugs. "A fast metabolizer of one drug," says Dr. Vesell, "will probably metabolize certain other chemically unrelated drugs in a similar fashion."

Researchers are finding that inherited adverse reactions to drugs can be traced to drug-metabolizing enzymes. Some of these enzymes are found in blood, others in the liver. So far it appears that such enzymes differ in their structure from the normal enzyme. Known pharmacogenetic conditions appear to adhere to the general principles established for inborn errors of metabolism. Of the almost 1,000 inherited metabolic diseases known, virtually all are triggered by structural changes in a protein or enzyme.

Only a few of the structural alterations in those proteins or enzymes involved in adverse drug reactions and inborn metabolic errors have been elucidated. Others have been roughly worked out. The entire amino acid sequences of many hemoglobins and several of the amino acid substitutions causing abnormal activity of the enzyme glucose-6-phosphate dehydrogenase are known. Persons with a variant G6PD enzyme are subject to hemolysis (the liberation of hemoglobin) when any one of a plethora of drugs is administered. Dr. Bert La Du of the New York University School of Medicine is making progress in unraveling the structure of the atypical pseudocholinesterase enzyme. Pseudocholinesterase catalyzes hydrolysis of aspirin, succinylcholine and other drugs. "So far," Dr. La Du reports, "we have electrophoretic evidence that two sites on the atypical enzyme have been modified. Both modifications, we believe, arose from a single amino acid change during enzyme synthesis. We're now trying to purify the atypical cholinesterase, to fingerprint it, then perform amino acid sequencing to see if we're right."

Most inborn errors of metabolism are caused by genetic defects occuring at a single genetic locus rather than in multiple loci. Traits controlled by genes at a single genetic locus obey Mendel's laws with respect to their transmission. An individual who inherits a double dose of a defective gene, that is from both parents, would exhibit lower enzyme activity than either parent. Where one or more genes determines a trait, though, an individual's enzyme activity, or his capacity to handle drugs, falls between that of his parents.

Individual genetic differences in en-



Penn State

Dr. Vesell: Genes control response.

zyme activity can also drastically affect the nature of an individual's drug interactions. If a person is a slow metabolizer of the drug isoniazid, for example, the drug would slow metabolism of the drug diphenylhydantoin if given at the same time, since the latter chemical is handled by a competing enzyme at some point in the metabolic pathway. Also, as a host of enzymes is probably involved in the absorption, induction, activation, conjugation and excretion of a drug, a defect in any one of these enzymes could drastically affect the metabolism of medications given simultaneously.

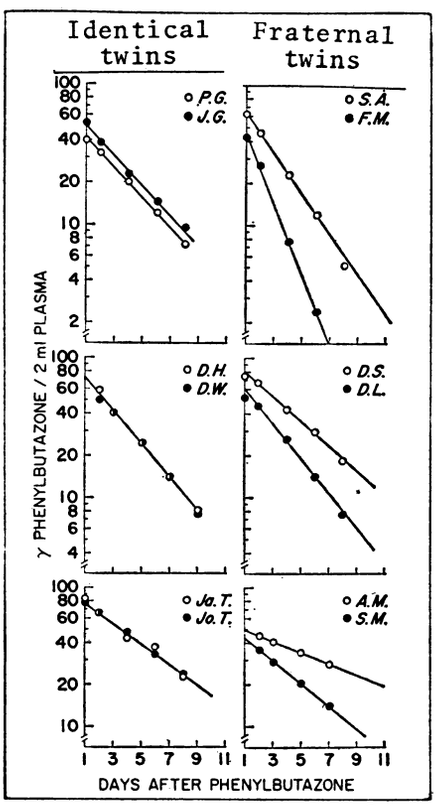
Clinical pharmacologists are bringing into medical practice the results of these recent discoveries in pharmacogenetics. The realm has expanded far beyond a few rare conditions produced after administration of select rare drugs. It is known that individual variations in response to many commonly used drugs are genetically controlled, and therefore should be considered as pharmacogenetic examples. Today every physician is aware that his patient falls somewhere on a broad bell-shaped distribution curve reflecting over-all population response to a particular drug.

Now, if the physician knew where his patient fell on that curve, he could estimate much more accurately the appropriate nontoxic dose of a drug to administer. To help him, assays for measuring the concentration of at least 50 different drugs in the blood are now available. To perform an assay for the concentration of a particular drug, the physician simply takes a small sample of blood from his patient. A widespread application of these assays, it is felt, would help diminish the current alarmingly high incidence of drug toxicity.

Physicians are becoming more aware of the usefulness of these drug assays. There is a trend now among clinicians to measure blood drug levels in patients and to guide therapy accordingly. If a patient suffers toxic reactions from a drug, the physician would probably take him off the medication. But by knowing whether a patient is a rapid or slow metabolizer of a drug, the physician might choose to alter drug dosage rather than take the patient off the drug, and he could make the decision according to blood drug concentration.

Blood enzyme tests are also telling physicians whether a person has a normal or an atypical pseudocholinesterase. A plasma sample containing the enzyme is placed in a spectrometer, where the activity of the enzyme towards its substrate is measured. Dr. La Du says that physicians are now at the stage of evaluating whether this assay should be used routinely on hospital patients, or selectively for certain high-risk populations, and in particular clinical situations. Some pharmacogeneticists advocate screening individuals who are to receive succinylcholine before surgery for their pseudocholinesterase activity. Many patients receive succinylcholine before surgery, and those with the atypical pseudocholinesterase would be at high risk, actually facing a severe threat to their life, if an anesthesiologist weren't standing by to give them artificial respiration.

Knowing how certain endogenous



Science

Response same in identical twins.

N.Y.U.

Dr. La Du: Enzyme structure critical.

materials, such as cortisone, are handled by an enzyme that also metabolizes drugs might likewise provide a convenient index to drug-metabolizing ability. Pharmacogenetics may also provide enlightenment about fetal genetic predispositions to drug reactions.

Although it is known that the human fetus has drug metabolizing enzymes (animal fetuses may not), no researcher has yet taken human fetal amniotic cells and grown them in culture to determine enzyme activity. However some pediatric researchers, such as Dr. Sumner Yaffe of Buffalo Children's Hospital and Henry Nadler of Northwestern University Medical School, are anticipating such scrutiny in the near future. Scientists might also assess some of the drug dangers to the fetus by examining the mother's genotype, Dr. La Du speculates. Drugs may have adverse effects on the fetus, not because of maverick drug-metabolizing enzymes in the fetus, particularly, but because there is something unusual in the way the mother handles the drug.

Ideally pharmacogenetics may bring the day when a patient, whether adult, infant or fetus, can be typed for response to different drugs, as patients are now typed for blood before being given a transfusion.

Essentially pharmacogenetics is a branch of the 50-year-old field of inborn errors of metabolism. Pharmacogenetics, Dr. La Du estimates, is about where inborn errors research was 40 years ago. "The cases we've studied so far," he says, "are the most obvious, the prototypes of others to come."

Nonetheless, given that the practical applications of pharmacogenetics are being pursued today only by a handful of investigators, impressive strides have been made since the first international pharmacogenetics symposium was held in 1967 (SN: 10/21/67, p. 392). At that conference researchers concurred that genetic makeup plays a definite, but as yet undefined role in a person's reaction to a particular drug. □