Custom-Designing Drug Doses to Fit the Genes

The same dose that is beneficial for one patient may be ineffective for another and deadly for a third. Scientists are learning more about the genetically programmed variations in metabolism that can lead to adverse drug reactions.

By LISA DAVIS

Recently, 108 children suffering from leukemia in a hospital in Tennessee were given an anticancer drug called methotrexate. In an effort to pinpoint the optimum therapeutic dose of the drug, as well as to cure the cancer, a team of physician-researchers at the hospital gave each child infusions of 1,000 milligrams of methotrexate per square meter of body surface, in a complex treatment regimen. They found, as reported in the Feb. 20 NEW ENGLAND JOURNAL OF MEDICINE, that though the doses were standardized, the drug concentration in each child's bloodstream varied as much as three-fold. And chances of survival turned out to depend in large part on the child having a high level of circulating drug.

Doctors use drugs as long-distance tools against diseases hidden inside bone and blood; medicine is a "practice," an inexact art. Perhaps nothing says more about the complexity of prescribing than that the researchers in this case aren't sure *why* there were such variations in drug level.

This isn't the first time doctors have been faced with the problem of unresponsiveness to a drug dose that is usually effective, or with the related problem of a catastrophic reaction to a generally well-tolerated drug. There are a host of elements that determine a patient's response to a drug, according to William Evans of the University of Tennessee in Memphis, who led the methotrexate study. Age, sex, diet, kidney efficiency and fat distribution — and the interactions of these and many other factors — can all affect drug metabolism. Increasingly, researchers like those in the methotrexate group are looking to the role of genes in drug metabolism to fill in some of the unknowns of prescribing.

"Many people take drugs on a certain prescribed basis, maybe two or three times a day," says pharmacologist Robert Smith of St. Mary's Hospital School of Medicine in London, England. "The assumption underneath it all is they're all going to handle the drug equally, and in many cases they don't." Pharmacogenetics pioneer Elliott Vesell, of Pennsylvania State College of Medicine in Hershey, adds, "Physicians are becoming more attuned to the necessity for individualizing drug doses. That's part of the art of being a good physician. . . . [Otherwise] they'll kill their patients."

Though the study of pharmacogenetics got its start in the '50s and '60s, a discovery by Smith about a decade ago dramatized the need to reckon with genes when prescribing even common drugs. Smith's investigation was prompted by his own collapse after taking a normal dose of a blood pressure medication he was studying.

"My blood pressure fell to 70 over 50. My colleagues were really concerned; they thought I was on the way out," Smith says. "Then we came round to analyzing what had happened, and we found that I was not metabolizing the drug."

Nearly untouched by the enzyme that normally degrades it into harmless parts, the drug, called debrisoquine, had reached levels in Smith's blood that "became very unpleasant, very quickly." The St. Mary's group tested the responses to small doses of debrisoquine in a group of 94 medical students and found two more "poor metabolizers," as Smith dubbed them. Says Smith, "When we tested the three families [his and the two students'], we knew we had a genetically determined deficiency."

What was going on in these debrisoquine hyperresponders? Studies by the St. Mary's group and others located the problem in a liver enzyme, one of a system of enzymes called the cytochrome p450s. According to Vesell, whose research on twins provided early evidence

Metabolism: Loading the dice for disease?

Therapeutic drugs are just a subset of a larger category that includes all the foreign chemicals with which the body must cope — chemicals in cigarette smoke, in food, at work. Research on drug metabolism is providing evidence that susceptibility to many major diseases is influenced by genetic variations, as well as by exposure to some of these chemical triggers (SN: 6/7/86, p. 358). The work is starting to make sense of a long-standing puzzle: What determines who will die of a disease, and who will survive? What determines who will get the disease in the first place?

"We still face the enigma of why one man smokes 40 cigarettes a day for 30 years and is quite okay, and his neighbor down the road will develop bronchial carcinoma in perhaps 12 years," says Robert Smith, a pharmacologist at St. Mary's Hospital School of Medicine in London, England. "There's good evidence now to suggest that bronchial carcinoma is associated with particularly rapid [metabolizers], who can activate carcinogens in smoke."

Lung cancer is an undeniable down side to rapid metabolism, but more often it is the slow metabolizers who are at increased risk of environmentally associated diseases. According to Smith, some of the latest work suggests that susceptibility to Parkinson's disease and rheumatoid arthritis may sprout from a genetic inability to handle environmental toxins.

After understanding may come prevention. "As we begin to understand more of the determinants of susceptibility — which probably won't be reasonably complete for another two lifetimes — we may be able to develop a type of genetic printout when we're born, [to] indicate those kinds of environmental insults to avoid because of our own biochemistry," says Edward Calabrese, a toxicologist at the University of Massachusetts in Amherst. "It's science fiction, but it's not that far from coming true."

— L. Davis

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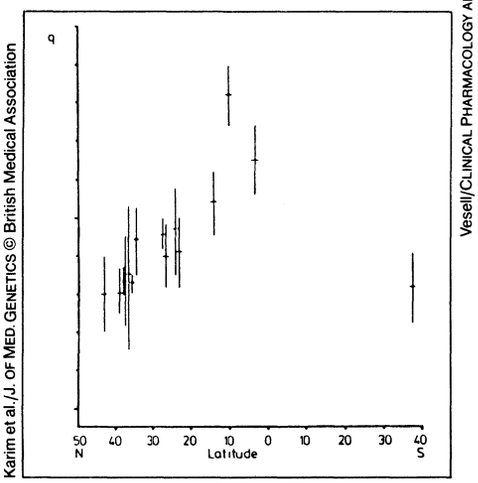
of genetic control of drug metabolism, there is still disagreement over whether the poor metabolizers have a less efficient form of the enzyme or lack it altogether, but it is clear that the enzyme's ability to oxidize chemicals is impaired in these people. And because oxidation is "the most common pathway of metabolism," Smith says, such a defect puts poor metabolizers at risk of adverse reactions to a number of drugs. A group at Sweden's Karolinska Institute, for instance, reported in the Feb. 6, 1982 LANCET that poor metabolizers show exaggerated responses to several betablockers that are used to decrease heart rate.



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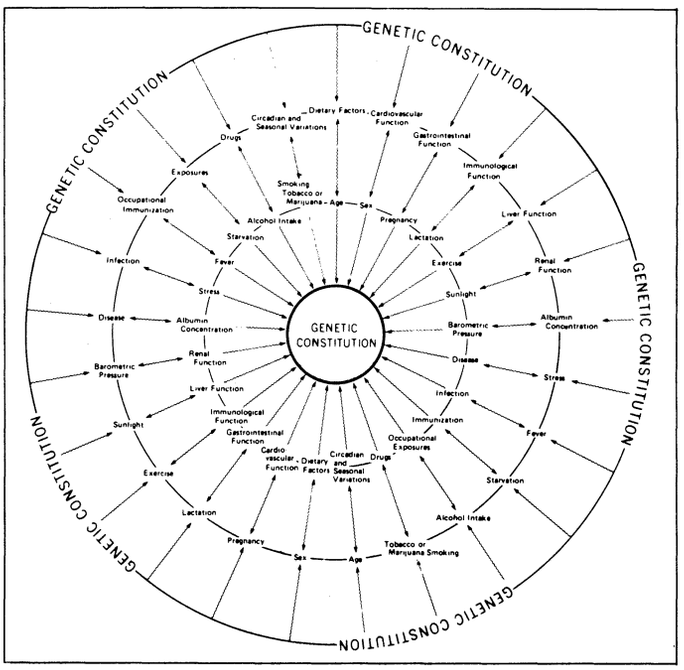
Researchers have attempted to discover rules explaining the differing proportions of problem metabolizers among populations. Here, a relationship between geographical latitude and the frequency of the gene for slow acetylation can be seen: In countries along the Pacific Rim, the closer a population is to the equator, the greater the proportion of slow acetylators. "This observation strongly suggests that the acetylation polymorphism is maintained by a process of natural selection," pharmacologist Werner Kalow writes. Similarly, there is speculation that the varying proportions of hyperresponders to the blood pressure drug debrisoquine among different ethnic groups – about 10 percent in Caucasians, 3 percent in Oriental populations, 1 percent in the Middle East – give a clue to the origin of the "poor metabolism" trait. London pharmacologist Robert Smith sees a "nice raison d'être" *in the idea that exposure to potentially toxic compounds in the diet may have been a selective pressure for the more efficient form of the oxidizing enzyme. For example, there are poisons in species of fish that humans can eat without harm, because the toxins are inactivated during digestion by a system of liver enzymes. The presence of such toxins in the diet of a fish-eating Oriental culture would have been a strong selective pressure, and, Smith speculates, could explain the lower frequency of the defective enzyme in that population.*



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A multitude of factors can affect response to a drug. The interactions are extremely complex, and though genetic make-up always modulates the impact of environmental factors, the balance can change day by day, according to pharmacologist Elliot Vesell.

Poor metabolizers may experience exaggerated responses to drugs left in a potent, unmetabolized form, or therapeutic failures with drugs that must be metabolized to become active. Often, these are effects that physicians can easily avoid, says Smith. In the case of a drug like debrisoquine, for instance, a precipitous drop in blood pressure signals the physician that the dose had better be adjusted.

But when drugs are not so easily "read" they can kill, as they did in England in the mid-1970s when doctors began prescribing a drug called perhexiline for chronic chest pain. In that case, there were no readily measurable signs to indicate whether the drug was behaving normally. It caused severe nerve damage in about 400 patients, and fatal liver damage in a few, before scientists realized what was going on. "There were no real overt signs of what was happening," Smith says, "until these people had accumulated 50 or 60 grams of drug in their tissues and the weakest links started to break."

The perhexiline episode pointed out a major weakness in drug development, according to Werner Kalow, one of the pioneers in pharmacogenetics, at the University of Toronto. Though drugs are tested in animals before they become available for clinical use, experimental animals are usually highly inbred to avoid the very kind of genetic variations that caused problems in humans taking the drug. Scientists at that time "didn't think of this kind of variation," Kalow says. "This is the main problem that we have. [And] drugs have been tested on too few people to find" genetic variations that occur infrequently.

Population studies done by the St. Mary's group showed that the debrisoquine defect is a recessive trait, caused by a single gene – only people who have inherited the gene from both parents will show its effects. Even so, millions of people in the world have this genetic impairment in their ability to oxidize chemicals. According to Kalow, the defect appears in about 10 percent of the Caucasian populations of the United Kingdom and Canada (and probably the United States as well), about 3 percent of Oriental populations and about 1 percent of Semitic populations.

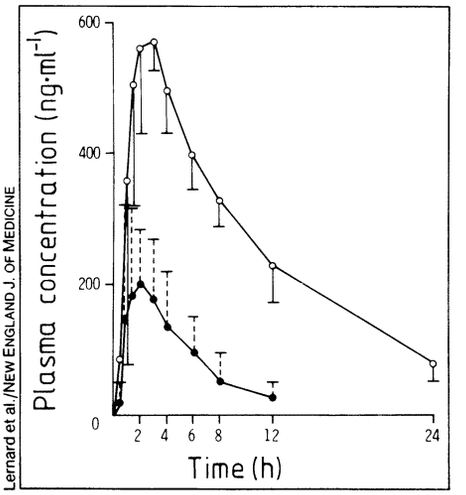
There are other types of problem metabolizers as well. Even before the debrisoquine discovery, scientists at the University of Cincinnati reported that another metabolic pathway, acetylation, showed genetically controlled variability. In this pathway, an acetyl group is added to a foreign chemical as part of the process of degradation. Research continues at Cornell University on the possible connection between slow acetylation and drug-induced or spontaneous systemic lupus erythematosus, a multisystem inflammatory disorder of uncertain origin. Researchers have found many other enzymatic variants, and, Vesell says, "we think there's much more genetic variation than we've discovered."

Though these genetic quirks in metabolism are clearly a potential problem for large numbers of people, when it comes to prescribing drugs some doctors may not be fully aware of the dangers, according to Smith. "There's still quite a long way to go in terms of education in these things. You have to bear in mind that the average practicing physician was trained 15, 20 years ago, and all these [discoveries] have happened in the last decade."

The problem metabolizer carries no distinguishing marks as he or she walks through a physician's door. If a needed

drug isn't widely known to be subject to variable metabolism, and if it accumulates without immediate and noticeable effect, complications may go unrecognized; or they may be ascribed to the disease, instead of to patient-drug interactions. Even the physician primed to recognize the adverse reactions of a problem metabolizer may not get the chance, since patients don't always come back after receiving a prescription.

The situation is exacerbated by the narrow therapeutic window of many of the newest, most powerful drugs. With some, like the anticonvulsant phenytoin, the effect may go from therapeutic to toxic with an increase of just 10 micrograms per milliliter blood concentration. In a poor metabolizer, a drug stays potent so long that it is as though a higher dose has been given; with these patients, a doctor may need to reduce the dose to one-tenth to get into the therapeutic window.



Blood concentrations of a betablocker – medicine used to reduce heart rate – are lower in patients known to be "extensive"• than in "poor"○ metabolizers of debrisoquine.

There are some new technologies that can help. Rapid, though expensive, blood tests are available that can tell the doctor how much of the drug has been metabolized. A growing number of hospitals and physicians use computer programs to flag drugs prone to variable metabolism, and help adjust doses for a problem metabolizer. These "pharmacokinetic" programs can also take into account other factors that may increase or decrease metabolic difficulties. For instance, cigarette smoking, according to pharmacologist Daniel Robinson of the University of Florida in Gainesville, who designed a pharmacokinetic computer program, "induces [patients'] enzymes in the liver to metabolize the hydrocarbons in the smoke, and just as a by-product of that they happen to metabolize certain drugs faster."

But the tool most widely used by physicians is the package insert, instructions provided by the drug company that note contraindications or other possible problems. The pharmaceutical industry has adapted rapidly to the last decade's discoveries in the field. Early in research, companies now investigate the pathways by which new drug candidates are metabolized, to see if the drug is prone to variable metabolism.

"The industry is interested to try to identify whether [genetic variability] affects their drug, so they can give the physician more guidance about attentiveness to prescribing," says Smith. "That's really the bottom-line message with this – we now know one of the discrete reasons why you need to individualize dosage."

Good physicians, of course, are already sensitive to the possibility of idiosyncratic responses with each patient. "The astute physician has always individualized dose; the astute physician has always looked at the patient to see the effect of the medication," Vesell says. "Each time, it's a guesstimate of the right dose.

"I think we have to recognize that giving drugs is nowhere near as precise as we would like it to be. In the future, it may be that everyone will be typed [for metabolic characteristics], when we get down to the DNA for these genetic defects, and will carry a card like they do for the blood groups. But until then physicians have to be very, very careful to get into the therapeutic window – out of the toxic and into the therapeutic range." □

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By Frances Tenenbaum

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