SCIENCE

Screening for Genes

Matching medications to your genetic heritage

By Sharon Begley

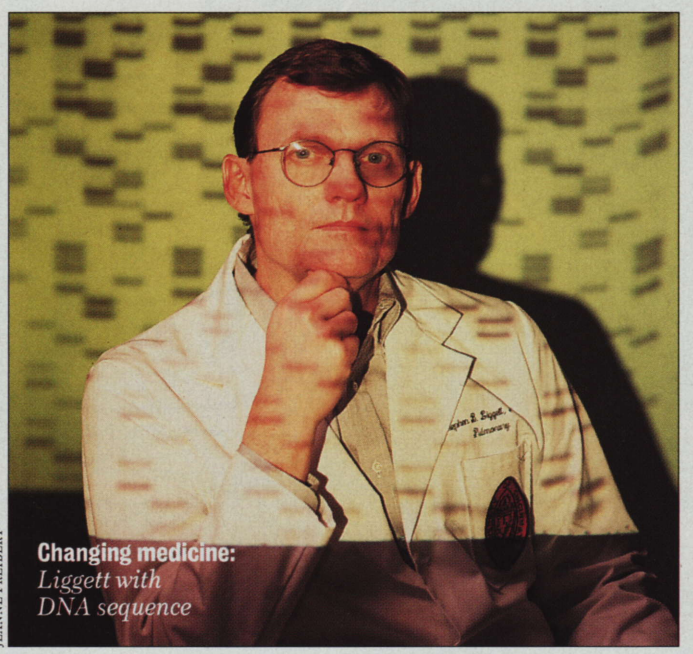
THE LITTLE BOY WAS ONLY 9, and he had leukemia. To his parents he was one in a billion, a little charmer whose life was slipping away. But to the doctors at the Mayo Clinic in Rochester, Minn., he was one in 300: the child belonged to the .3 percent of the population who carry a gene leaving them unable to properly metabolize a whole family of drugs. One of the drugs, a member of a class of medications called thiopurines, is prescribed for childhood leukemia. But doctors at the boy's first hospital didn't check him for the gene. They just started him on the drug. It built up in his body to toxic levels, and wiped out his bone marrow like a toxic spill wiping out a meadow. He was rushed to Mayo for a bone-marrow transplant—the victim of a mismatch between his genes and the medicine meant to save his life.

License plates are personalized, exercise routines are individualized, even Levi's can be custom cut. The poisoned boy shows that medicine, too, needs to abandon the one-size-fits-all approach to drugs. Slowly, with infusions of sophisticated genetics and biotechnology, it is doing just that. Working in the new field called pharmacogenetics, scientists are making discoveries that link particular genes to how patients will respond to medication—specifically, whether the drug will help them and whether they will suffer side effects. The research, says Dr. Michael Kauffman of the biotech firm Millennium Predictive Medicine, promises to "change the practice of medicine."

That practice could use some shaking up. According to a 1998 study in The Journal of the American Medical Association, 2.2 million patients a year have adverse reactions to drugs; 106,000 of them die. Many millions more simply aren't helped, and geneticists are tracking down why. Basically, it comes down to misspellings. If you think of a gene as a string of thousands of molecules in varying combinations of the letters A, T, C and G, even one wrong letter can mean trouble. The cholesterol-lowering drug pravastatin won't work in people with a common misspelling of one gene. Clozapine, a drug for schizophrenia, is less likely to help patients who have two copies of a certain spelling of another gene; in 1 percent of patients, the combination of misspelling and drug can be fatal. Procainamide, a drug for heart arrhythmias, can cause a sometimes fatal liver disease in people whose genes make them slow to carry out a certain biochemical reaction.

Though few doctors take a patient's genetic profile before whipping out their little white pad, that's beginning to change. At the Mayo Clinic, "it is now a standard clinical test" to see if patients carry the misspelling that leaves them unable to detoxify the thiopurine drugs, says Dr. Richard Weinshilboum. But that is not so everywhere. Although the 9-year-old who wound up at Mayo recovered and was sent home at Christmas, the failure of another hospital to do the $150 test almost killed him. The first misspelling to be widely tested for could be one that affects asthma drugs. Drugs called beta-two agonists, which include Ventolin and Albuterol, act on molecules in the smooth muscle of the lungs. The molecules control the opening and closing of the bronchial tubes, which are constricted in asthma. The gene that makes the molecule has at least two spellings, says Dr. Stephen Liggett of the University of Cincinnati Medical Center, "and you'll have a different response to these drugs depending on which one you have." With one spelling the drug is almost useless, and the asthmatic can land in the ER gasping for breath. "We are right at the precipice of establishing gene type as soon as we diagnose asthma," says Liggett, whose lab can do the genetic analysis for $2.

The pharmaceutical industry, however, is deeply divided over this approach. Abbott and Pharmacia & Upjohn are collecting data that will let them match some of their new drugs to patients' genetic profiles. But other companies worry that if only patients with certain genes are given a particular drug, then their markets will shrink. But George Post, of pharmaceutical giant SmithKline Beecham, thinks that the fear of litigation will drive pharmacogenetics. "Imagine," he says, "a lawyer asking, 'Doctor, did you know this drug would kill your patient? Did you know there is a test that would have predicted that? And why did you not give your patient that test?' " If pharmacogenetics lives up to its early promise, there won't be any easy answer to that. ■



JEANNE FREIBERT

Changing medicine: *Liggett with DNA sequence*

Prescription for Disaster

Every year, more than 100,000 people die in the U.S. because they carry "misspelled" genes that make medications either ineffective or deadly. Now doctors can test for the genes before prescribing.

DRUG	USE	EFFECT OF MISSPELLED GENE
Albuterol, Ventolin	Asthma	Makes medication ineffective, leading to gasping, wheezing
Thiopurines	Childhood leukemia	Drug is not metabolized; its buildup kills bone marrow
Codeine	Pain	Body can't convert drug to its active form; no pain relief
Isoniazid	Tuberculosis	Body metabolizes drug so fast it isn't absorbed
Prozac	Depression	Drug is metabolized so slowly it can reach toxic levels
Procainamide	Heart	Drug isn't cleared from body, leading to fatal liver disease