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PROSPECTS

Gina Kolata

A Tale of Two Drugs Hints at Promise for Genetic Testing

A decade or so ago, when the revolution in genetics was getting under way, the air was heady with promises.

Gene tests, scientists predicted, would become an integral part of drug prescribing. No longer would patients find out too late that a drug did not work for them. No longer would they have to wait to see if they had side effects to one drug before switching to another.

Tests of their genes would make all of this clear. But with the exception of a few tests for genes on certain cancer cells, the

genetics revolution has not yet happened.

There are many reasons. But the stories of two drugs — one for heart failure, the other for breast cancer — illuminate some of the difficulties as well as the immense promise that is still to come.

Now maybe, just maybe, the promised revolution is imminent.

"We are sitting here on the edge of a very significant improvement" in drug therapy, said Dr. David Flockhart, a professor of medicine, genetics and pharmacology at Indiana University. "It involves

no new drugs, no massive drug development program. It involves exploiting natural human variation to protect people from therapy when it will be useless."

One story begins with a drug that was wholly abandoned: bucindolol, a once-promising treatment for heart failure.

Bucindolol, one in a class of drugs known as beta blockers, was tested in a large study sponsored by the National Heart, Lung and Blood Institute and the Department of Veterans Affairs.

But the clinical trial was halted early af-

ter research on other beta blockers found that those drugs improved survival for most heart failure patients. The researchers studying bucindolol felt that, given these findings, it would have been unethical to continue the study because it meant giving some patients a placebo.

Soon, bucindolol was all but forgotten. But even if beta blockers help most heart failure patients, they do not help all, and Dr. Stephen Liggett, who researches heart

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failure at the University of Maryland School of Medicine, wanted to understand why.

Heart failure affects more than five million Americans, and it is a dire illness. It takes six months to a year of beta blocker treatment before it is clear whether the drugs are helping. With heart failure, Dr. Liggett says, a year is too long to wait.

The hallmark of the illness is a damaged heart, from a heart attack, viral infection, high blood pressure or unknown causes. Struggling to pump blood, the heart grows, sometimes getting so large that it fills a patient's chest.

Soon the lungs fill with fluid, and, with congested lungs and a heart that can barely pump, patients become so short of breath that they cannot walk across a room. Half die within five years.

Those who respond to beta blockers, Dr. Liggett proposed, may have a slight variation in a gene that determines the structure of a protein on heart cells where the drugs attach.

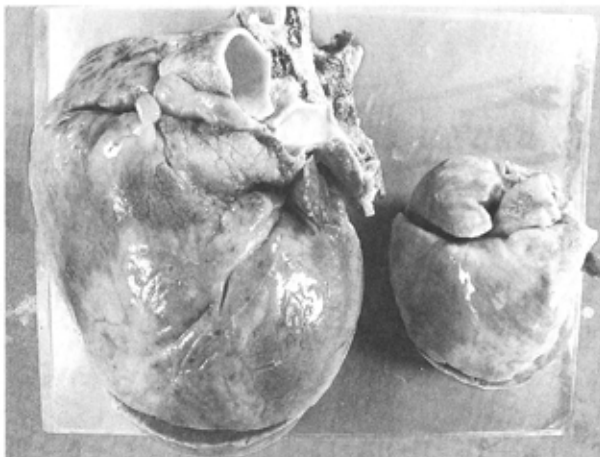
In the meantime, Dr. Michael Bristow of the University of Colorado Health Sciences Center found himself unable to give up on bucindolol. Poring through the clinical trial data, he was convinced that some patients were substantially helped, even more than they were by other beta blockers.

But it was not clear how to identify those patients in advance.

It turned out, though, that the bucindolol trial was unique in heart disease research. Genetic material is not obtained from patients in most studies, but the researchers who conducted the bucindolol trial insisted that the participants' DNA be collected and stored.

Dr. Bristow and Dr. Liggett realized that they had a chance to test Dr. Liggett's hypothesis.

They could go through the trial



Bob Katus/International Registry of Pathology

IN CONTRAST A failed heart, left, and a normal one. Genetic tests might be used to identify patients who can be helped by certain drugs.

data and ask whether the gene variants identified responders and non-responders to the drug.

The gene tests succeeded, as the investigators report this week in *The Proceedings of the National Academy of Sciences*. Responders not only did well with bucindolol, having a 38 percent reduction in their death rate, but they also did better than patients who were taking beta blockers that are already on the market.

Now Dr. Bristow wants to resurrect bucindolol. He has licensed it, formed a company, Arca Discovery, and hired Dr. Liggett as a consultant. He is applying to the Food and Drug Administration to market the drug along with a genetic test.

But what if bucindolol was marketed with the genetic test and the test also identified people who would do better with the beta blockers currently on the market? Which drug should they take? Should nonresponders take any beta blocker at all?

copy of the variant gene, have a greatly reduced ability to activate it.

"These are huge effects — 100-fold differences in activity," Dr. Flockhart said.

He wonders, he said, if tamoxifen is restricted to responders whether it may actually be more effective than the newer drugs called aromatase inhibitors. Those drugs, unlike tamoxifen, are still under patent and are heavily marketed by their manufacturers as being 2 to 3 percent more effective than tamoxifen. But who will pay for such a comparative study?

In the meantime, the evidence that the gene test could completely determine tamoxifen's clinical outcomes is not ironclad. "We have one clinical trial that says it is the case," Dr. Flockhart said.

Although there have been many clinical trials of tamoxifen, none collected DNA data. So it is impossible to go back, as Dr. Liggett and Dr. Bristow did, and ask if the gene test predicted whether a woman's cancer was more likely to recur if she could not activate tamoxifen.

Dr. Flockhart, for one, bemoans the opportunities lost because DNA was not stored in clinical trials in the past. "It really is an indictment of the oncology community," he said.

Dr. Richard Weinsilboum, a pharmacogenetics researcher at the Mayo Clinic, said that may be changing. More and more studies are collecting and storing participants' DNA, and there is increasing interest in looking for genetic variations that may determine whether a person responds to a particular drug.

The change has been a long time coming, Dr. Weinsilboum added.

"It has frustrated me to see the pace," he said. "Sometimes from my perspective, it has been a glacial pace. But I think we have to be patient. Those of us who do the research are sometimes the least patient in trying to get the research out." But, he added, "We want to be sure it's right."