The Beginnings: Laboratory and Animal Studies

The scene is a typical one. A patient, perhaps you or I, goes to a doctor and gets a prescription. Then a pharmacist fills the prescription, with instructions to take the drug in the prescribed amount and manner over the following days, weeks or months. This scene is repeated millions of times across this country every day—some 2 billion prescriptions are filled every year in the United States. In fact, the process is so commonplace that the pills, tablets, capsules, and other medications that virtually every one of us relies on to restore or maintain good health at some point in our lives come to be taken for granted.

Yet these drugs—and the improved quality of health they bring to the American people—are truly “miracles of modern science.” In fact, the process for discovering, developing and testing new drugs encompasses some of the most exciting areas of scientific discovery today. The endeavor runs the gamut from basic biomedical investigation of living cells and molecules to applied research that yields new consumer products to improve healthcare.

The Cutting Edge

“We are on the cutting edge of the biological sciences,” says Rhoda Gruen, Ph.D., special assistant to the president of international research and development at Hoffmann-La Roche, Inc., a pharmaceutical research and manufacturing firm headquartered in Nutley, N.J. “We suck up new information like a sponge. Everything we do is subject to change as new scientific information becomes known.”

The research process is a complicated, time-consuming, and costly one whose end result is never known at the outset. Discovering a new drug has been likened to searching for the proverbial needle in a haystack. Literally hundreds, and sometimes thousands, of chemical compounds must be made and tested to find one that can achieve the desirable result without too-serious side effects.

The complexity of the process can be gauged, in part,
by the diversity of scientific disciplines engaged in finding new drugs. Traditional organic chemists, physiologists and statisticians have been joined in recent years by new kinds of specialists. Biochemists study the chemistry of life processes. Molecular biologists study the molecules that make up living matter. Toxicologists investigate chemicals’ potential for harm. Pharmacologists look at how drugs work. And computer scientists apply the power of their sophisticated machines to analyze and assess new chemicals. Each provides a different way of looking for that needle.

Such a complicated process costs vast amounts of time and money. FDA estimates that, on average, it takes eight-and-a-half years to study and test a new drug before the agency can approve it for the general public. That includes early laboratory and animal testing, as well as later clinical trials using human subjects.

Drug companies spend $359 million, on average, to develop a new drug, according to a 1993 report by the Congressional Office of Technology Assessment. A company such as Hoffmann-La Roche, whose annual sales in the United States alone are about $3 billion, spends about $1 billion a year on research worldwide.

Building on Good Science

There is no standard route by which the thousands of drugs now sold in the United States were developed. “Each drug has its own way of being born,” says Clement Stone, a former senior vice president for Merck and Co. Inc., research laboratories, in West Point, Pa. “Often, we consciously search for a drug for a specific use, but more often, it is serendipity. What is required, though, is good science building on good science.”

In some cases, a pharmaceutical company decides to develop a new drug aimed at a specific disease or medical condition. In others, company scientists may be free to pursue an interesting or promising line of research. And, in yet others, new findings from university, government, or other laboratories may point the way for drug companies to follow in their own research.

Indeed, the process typically combines elements of all three avenues. New drug research starts by studying how the body functions, both normally and abnormally, at its most basic levels, Ronald Kuntzman, vice president for research and development at Hoffmann-La Roche, says. The pertinent question is: “If I change it [the body’s functioning], will I have a useful drug?” That, in turn, leads to a concept of how a drug might be used to prevent, cure, or treat a disease or medical condition. Once the concept has been developed, the researcher has a target to aim for, Kuntzman adds.

Gruen elaborates: “Disease processes are complex and involve a sequence of events. If you want to intervene in the disease process, you try to break it down into its component parts. You then analyze those parts to find out what abnormal events are occurring at the cellular and molecular levels. You would then select a particular step as a target for drug development with the aim of correcting the cellular or molecular dysfunction.”

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A Cholesterol Drug

Take cholesterol, a waxlike substance found naturally in the body. Too much cholesterol, either naturally or in the diet, can cause it to build up on the inside walls of blood vessels. This can clog the arteries that deliver blood to the heart muscle, blocking the flow of oxygen and nutrients, causing a heart attack.

There have been few drugs that effectively cut cholesterol levels without either toxic or unpleasant side effects. This has limited their use. Others that were tested acted too late in the process by which the body makes cholesterol to lower its levels. What was needed, says Eve Slater, M.D., executive vice president for worldwide regulatory affairs for Merck, was a drug that would act earlier in the cholesterol-making process.

To find one, scientists at Merck and elsewhere spent decades studying how the body makes and uses cholesterol. Along the way, they identified more than 20 biochemical reactions necessary for the body to make cholesterol, along with the enzymes required at each step to turn one chemical into
the next one in the chain.

The research problem, Slater says, was to find the step where interference by a drug would effectively lower cholesterol production. By the 1970s, scientists had found a possibility. They had isolated a chemical, mevalonic acid, which was an early link in the cholesterol chain, and an enzyme called HMG-CoA reductase, which produced mevalonic acid.

What was needed, then, was a drug that could either inhibit HMG-CoA reductase or prevent cells from correctly using the enzyme.

Sometimes, scientists are lucky and find the right compound quickly. More often, Gruen says, hundreds or even thousands must be tested. In a series of test tube experiments called assays, compounds are added one at a time to enzymes, cell cultures, or cellular substances grown in a laboratory. The goal is to find which additions show some chemical effect. Some may not work well, but may hint at ways of changing the compound’s chemical structure to improve its performance. The latter process alone may require testing dozens or hundreds of compounds.

Computer Clues

A more high-tech approach is to use computers to simulate an enzyme or other drug target and to design chemical structures that might work against it. Enzymes work when they attach to the correct site on a cell’s membrane. A computer can show scientists what the receptor site looks like and how one might tailor a compound to block an enzyme from attaching there.

Nevertheless, “computers give chemists clues to which compounds to make, but they don’t give any final answers,” says Kuntzman. “You still have to put any compound you made based on a computer [simulation] into a biological system to see if it works.”

Yet a third approach involves testing compounds made naturally by microscopic organisms. Candidates include fungi, viruses, and molds, such as those that led to penicillin and other antibiotics. Scientists grow the microorganisms in what they call a fermentation broth, one type of organism per broth. Sometimes 100,000 or more broths are tested to see whether any compound made by a microorganism has a desirable effect.

In the search for a new cholesterol drug, scientists found a fungus that inhibited the HMG-CoA reductase enzyme in a test tube. Chemists then had to identify which of the fungus’s dozens of chemical by-products was actually inhibiting the enzyme. Once that was done, the chemical’s structure was analyzed and improved to enhance its effects.

To this point, the search for a new drug has been confined to a laboratory test tube. Next, scientists have to test those compounds that have shown at least some desired effects in living animals. “We have to find what the drug is doing on the down side,” Kuntzman explains.

Animal Testing

In animal testing, Kuntzman says, drug companies make every effort to use as few animals as possible and to ensure their humane and proper care. Two or more species are typically tested because a drug may affect one differently from another. Such tests show whether a potential drug has toxic side effects and what its safety is at different doses. The results “point the way for human testing and, much later, product labeling,” Kuntzman says.

So far, research has aimed at discovering what a drug does to the body. Now, it must also find out what the body does to the drug. So, in animal testing, scientists measure how much of a drug is absorbed into the blood, how it is broken down chemically in the body, the toxicity of its breakdown products (metabolites), and how quickly the drug and its metabolites are excreted from the body. Sometimes, such tests find a metabolite that is more effective than the drug originally picked for development.

Of particular concern is how much of the drug is absorbed into the blood. “If a drug’s active ingredients don’t get into the blood,” Kuntzman says, “it won’t work.” Scientists may add other chemicals to the drug to help the body absorb it or, on the other side, to prevent it from being broken down and excreted too soon. Such changes in the drug’s structure mean even more testing.

Absorption rates can cause a host of problems. For example, for a certain drug to be effective, 75 percent of it may need to reach the bloodstream. But absorption rates can vary among individuals from, say, 10 to 80 percent. So, the drug must be able to produce the desired effects in those who absorb only 10 percent, but not cause intolerable side effects in people who absorb 80 percent.

“If we can improve the absorption rate we can reduce the variation in what real dosages people would be subject to,” Kuntzman says. A more standard absorption rate for all individuals, say around 75 to 80 percent, would mean that the dose could be reduced and still have the desired effects.

The Wrong Road

By this time in the testing process, many drugs that had seemed promising have fallen by the wayside. More often than many scientists care to admit, researchers just have to give up when a drug is poorly absorbed, is unsafe, or simply doesn’t work. “In research you have to know when to cut your losses if you are going down a wrong road,” says Clement Stone. And, he adds, there are many more wrong roads than right ones.

Nevertheless, progress may yet be
made. Occasionally, Stone says, a stubborn scientist keeps looking and finds a usable compound after others had given up. In other cases, compounds may be put aside because they failed to work on one disease, only to be taken off the shelf years later and found to work on another.

Such was the case with Retrovir (zidovudine, also known as AZT), the first drug approved for treatment of AIDS. The drug was first studied in 1964 as an anticancer drug, but it showed little promise. It was not until the 1980s, when desperate searches began for a way to treat victims of the AIDS virus, that scientists at Burroughs Wellcome Co., of Research Triangle Park, N.C., took another look at zidovudine. After it showed very positive results in human testing, it was approved by FDA in March 1987.

Even so, “a minuscule number of drugs we test ever reach testing in man,” says Richard Salvador, Ph.D., a Hoffmann-La Roche vice president and international director of preclinical development. The organization Pharmaceutical Research and Manufacturers of America estimates that only five in 5,000 compounds that enter preclinical testing make it to human testing, and only one of those five may be safe and effective enough to reach pharmacy shelves.

FDA’s Role

The role of FDA in the early stages of drug research is small. The Federal Food, Drug, and Cosmetic Act requires FDA to ensure that the new drugs developed by pharmaceutical companies are safe and effective. It does not give the agency responsibility to develop new drugs itself. So, FDA physicians, scientists, and other staff review test results submitted by drug developers. FDA determines whether the drug is safe enough to test in humans and, if so—after all human testing is completed—decides whether the drug can be sold to the public and what its label should say about directions for use, side effects, warnings, and the like.

FDA first becomes involved when a drug company has completed its testing in animals and is ready to test a drug on humans. (Actually, some animal testing continues after human tests begin to learn whether long-term use of the drug may cause cancer or birth defects. Also, more animal data may be needed if human tests turn up unexpected effects. And new therapeutic uses may be found by continued animal studies.)

Although FDA usually does not tell drug companies what specific laboratory or animal tests to run, the agency does have regulations and guidelines on the kinds of results FDA expects to see in any request to conduct human testing.

And the drug companies listen to those signals. Both Hoffmann-La Roche’s Kuntzman and Merck’s Stone say their companies follow and sometimes exceed FDA’s guidelines. “We want to optimize our chances of taking a compound from animal to human testing,” Stone says.

So drug research is a long, difficult, and costly road, certainly. But sometimes the hard work, the scientific sleuthing, and the time and dollars spent pay off. Such was the case in December 1992, when FDA approved Taxol for treatment of advanced cases of ovarian cancer in five months. Taxol is an important second-stage drug for ovarian cancer because, while most patients respond to chemotherapy initially, the disease often recurs.

But to scientists like Kuntzman, drug research goes even beyond preventing or curing diseases or making money. It is also a tool for finding out more about the human body and its basic life processes.

“Research is an evolutionary process,” Kuntzman says. “You change studies and use experiments to lead to other experiments. As you go along you may not even see the connection between studies. In a sense, research has no end. The only end would be when we understand everything there is to know about the human body. I expect that we will never know enough about the body.”

Merck’s Slater agrees. “We can make progress,” she says, “but we are unlikely to achieve perfection.”

In the end, that is what researching and developing new drugs is all about—understanding and progress.

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