CHEMISTRY

Man-Made Quinine

For the first time in history, this precious drug has been produced without the aid of a tree. With malaria spreading, this discovery is timely.

By HARLAND MANCHESTER

➤ EIGHTY-EIGHT YEARS ago a young man named William Perkin spent his Easter vacation in his attic laboratory in London trying to duplicate in a test-tube the quinine that comes from tree-bark. Malaria was ravaging the world, as it is today, and as usual there was a shortage of quinine. Before his vacation was over, the 18-year-old Perkin had discovered the first coal-tar dye. Thus he founded the organic chemical industry, and he became Sir William, but he never did synthesize quinine. That remained a kind of Holy Grail for aspiring chemists.

So it remained until Easter this year, when two young men named Robert W. Woodward and William E. Doering also spent their vacations in a laboratory, and finally succeeded where Perkin and many other brilliant scientists had failed. Starting with chemicals which can be made either from coal or petroleum, they copied the complicated structure of the quinine molecule and emerged with a small vial of the precious drug. It is not a substitute or an approximation; it *is* quinine, produced for the first time in history without the aid of a tree.

Very Timely

No discovery was ever more timely. Even before the war, the world malaria total ran to 800,000,000 cases and 3,000,000 deaths a year, and the cost of malaria to the United States alone was set at half a billion dollars annually. Despite the best medical care in the history of warfare, malaria is spreading, and health experts warn that because of great war migrations and faster transportation it may again menace areas where it was once under control. The cinchona groves of Java, which produce nearly all the world's quinine, are in the hands of the enemy, and our stockpile cannot last forever. The program for repatriating the cinchona tree in the Western Hemisphere will take many years, and, despite the use of atabrine and other substitutes, it is widely held that nothing can take the place of quinine itself. Few discoveries in the history of medicine offer greater potential promise than the tiny mound of crystals which materialized last April in Cambridge, Massachusetts.

Everyone connected with the Cambridge achievement is young. Robert Woodward and William Doering, who did the job, are 27 and 26. Edwin H. Land, scientist and manufacturer who backed the project, is 35.

Polarized Light

The story really begins ten years ago, when Land invented a way of aligning crystals of quinine and iodine in a transparent plastic sheet. This cheap material polarized light just as efficiently as the scarce and enormously expensive calcite crystals theretofore used. Land founded the Polaroid Corporation, and his sheets found an amazing variety of uses, from sun glasses to naval instruments. Soon he became one of the largest non-medical users of quinine in the country.

As early as 1931, when the Japanese invaded Manchuria, Land saw that our supply of quinine was threatened. He began experimenting with new light polarizers in which the crystals from cinchona bark would not be needed. The possibility of synthesizing quinine was of course discussed, but the success of such a project depended upon finding a chemist with a brain like Pasteur's or Ehrlich's, so this solution was dismissed. Finally a substitute polarizer was found which was even better than the quinine-crystal sheet.

But Land did not lose interest in quinine. Research plays an all-important part in his business, and he keeps on his payroll a number of part-time consulting chemists who teach or study at neighboring colleges. If one of these men has a pet project which looks promising to Land, he sometimes tells him to go ahead with it on the company time, even if the project doesn't look like an immediate money-maker. One such consultant was Dr. Woodward, who teaches at Harvard and who played a part in making the new quinine-less polarizer. Woodward couldn't get synthetic quinine out of his mind.

"I believe quinine can be synthesized," he told Land calmly, "and I believe that I can do it."

Woodward is a slender, bespectacled Boston-intellectual sort, the last man on earth to brag. He speaks mildly, but his words reveal a tough self-confidence, and people believe what he says. Land believed him, and in view of the record he had plenty of reason. Woodward was a ball of fire at the Massachusetts Institute of Technology, where teachers not given to fulsome praise called him "first in a class of one." Since knee-pants days he had worked in his home laboratory. After a year at M.I.T., where he did chores to defray his expenses, he was given a fellowship and his own laboratory to work in, and soon he was told to forget about classes and go on as he pleased. After four years' work he became a Ph.D. at the age of 20—a thing previously unheard of at M.I.T. After that he did further work at Harvard, and then joined the faculty.

"Road Map"

Encouraged by Land, Woodward prepared a brief plan for one of the most difficult and elaborate jobs in the history of chemistry. "It was a kind of road map in ten pages," says Land, "which charted a likely course through a long stretch of unknown terrain. He knew he might have to detour around swamps or mountains, so to speak, but he had a clear sense of direction, and anyone who knew Woodward would believe that he had a good chance of getting through. So I told him to go ahead."

One thing Woodward insisted upon. Bill Doering, a friend of his at Harvard, had to help him. Put Doering in a laboratory and he thinks the way Woodward does, but there the similarity ends. He was born in Texas, is full of bounce and ginger. He is openly delighted at the victory of his team, and dramatizes a diagram of the quinine molecule as though he were presenting Rita Hayworth. He is a natural complement to his reserved, matter-of-fact partner.

The two men set to work on February 1, 1943. Before them was a wooden model of the fantastically complicated quinine molecule which they were determined to duplicate. Fify-two balls, variously colored to represent the atoms of carbon, hydrogen, nitrogen and oxygen which make up the molecule, were joined in a crazy, asymmetrical pattern by means of short sticks. This two-foot model is a 150-million-times magnification of what scientists believe the quinine molecule resembles, judging by its behavior in various tests. If you alter the position of a single one of those 52 little spheres, you no longer have quinine.

Started from Toluol

Woodward and Doering started with a chemical called 7-hydroxyiso-quinoline, which comes easier after you say it three times. This chemical is obtained from toluol (basis of TNT) and acetylene, both of which can be derived from coal or petroleum. It is composed of the same types of atomic building blocks as quinine, but its molecule is radically different from the quinine molecule. The task facing Woodward and Doering was to take this molecule and figuratively juggle the balls and sticks around until they had precisely duplicated the pattern of the quinine molecule.

To the layman, this is like trying to build a four-masted schooner in a bottle in the dark. Perkin had tried to do the job by simply adding and subtracting atoms until he had the right number of each kind, hoping that in some way they would arrange themselves correctly. He might as well have thrown a galley of type from his attic window in the fond hope that it would set iself up into a telephone book when it hit the street.

Two Parts

Following Woodward's "road map," the two men first imagined that they had carved the quinine molecule into two parts, then set out to duplicate each part separately. Months were spent in erecting what Doering calls a chemical "skeleton" of the molecule, to which the details could be added later by means of infinitely patient carpentering jobs. Woodward teaches organic chemistry at Harvard, and could work only part time on the project, but Doering had just finished a secret war assignment and was free to experiment day and night. They were greatly relieved when summer vacation came, for then they could really get to work.

Starting with five pounds of the stuff with the long name, they put it through 15 major processes. They tortured it in stills under high pressures and temperatures to force new atoms into it, and after each step they had to put it through a new process to rescue the stuff that had "jelled" as it should, and get rid of the residue. In October, Doering took a teaching job at Columbia, and the partners had to collaborate at long distance, getting together weekends whenever possible to talk things over.

They were near the end of the road last March when they got a shock that nearly sank them. They finished the "prefabricated" sections of their quinine molecule, and sent one section to an outside laboratory for a test before trying to join the sections. In the wooden model, some of the atoms are connected by two parallel rods, and unless these "double bonds" are in exactly the right place, what you have is not quinine. When the result of the test came in, it showed that one double bond was in the wrong place.

Mistake Made

"We were ready to pack up and go home," says Doering. "But we couldn't see how we had slipped, and asked them to try again. We could hardly eat or sleep while we waited for the result. Well, the laboratory found that a mistake had been made in the testing method. They did another test, and we were right. That double bond was exactly where it should be."

Their work was saved, but they were nervously shot to pieces. Woodward phoned Doering at Columbia.

"Do you think you can finish it?" he asked.

"Do you think *you* can finish it?" countered Doering.

They were within sprinting distance of the tape, but neither had the strength to go on alone. Then Easter vacation arrived, Doering joined Woodward in Cambridge, and together they entered the last lap. They had a sort of now-or-never feeling about the venture, and drove themselves without mercy in a race with the flying days of "vacation."

Their records show that during nine days they worked a total of 110 hours, and that for six days in a row they stuck to the job until 2 a.m.

They knew that once they obtained quinotoxine, a close *(Turn to page 380)*

Do You Know?

Sulfathiazole, used in the treatment of inflammation of the tonsils, is now put up in chewing gum form.

The Mexican *huaraches,* a sandal-type footwear with a leather or woven henequen sole, are generally worn in rural districts and have distinctive designs which indicate the home section of the wearer.

Our 1943 *alloy steel* production alone was as great as Japan's total steel-making capacity.

During 1943 the United States shipped under *lend-lease* 11% of its lamb and mutton and over 15% of its pork supply.

A new *mulberry tree* has been developed for rearing silk worms in Latin America which produces a crop of leaves in six months.

Possible production of concentrated *superphosphates* for fertilizers without the use of sulfuric acid, by a method which employs phosphoric acid, is under investigation in Eire's emergency scientific bureau.

Milk requirements of the military services are nearly 50% larger than in 1943.

There is enough *aluminum* in the JRM-1, largest of the world's cargo planes, to make 100,000 saucepans.

Two-thirds of the nation's *traffic* is moved by railroad.

Helium is used in the treatment of asthma, tuberculosis, and other respiratory diseases.

Sugar goes into bombs, hand grenades and plastics—via industrial alcohol.

A new material for *luggage* is blotting paper impregnated with synthetic rubber to add toughness.

Estimates of the number of different kinds of *insects* in the world range from 600,000 upward.

Wheat is older than the history of man.

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relative of quinine, they could coast home, for back in 1853 Louis Pasteur had converted natural quinine into this material, and later, Rabe had changed it back to quinine. Late one night on the last day of vacation the stuff they had battered away at for more than a year turned to a dirty brown oil. This was a mixture of two kinds of quinotoxine, one of which yields quinine. Separating the two was a tricky job. After long preparation, they tried an acid used by Pasteur in dealing with a closely related substance. Nothing happened, and there was another agonizing moment.

Shot in the Dark

Then, by some sort of chemical intuition, they tried a shot in the dark, using a different acid. It worked, and a beautiful spectacle slowly took shape—fine yellow, interlaced needles of the quinine-yielding quinotoxine, the first ever made by man. Quinine itself was now in the bag, since they had only to follow in the footsteps of Rabe.

The next morning there were a few loose ends to pick up, and finally, after 14 months and ten days of concentrated work, the job was done. For the information of future engravers, the hour was 11 a.m., and the date Monday, April 10, 1944. It was, incidentally, Bob Woodward's 27th birthday.

Although Woodward and Doering have made a chemical discovery of the first magnitude, they are quick to point out that if the quinine they have constructed is to be made in quantities for medical use, the work has just begun. It is all very well to say that quinine can now be made from coal tar, and coal tar is cheap, but that proves nothing to a chemist. Woodward cautiously speaks of the loss of material along the way as they followed his tortuous "road map." Starting with five pounds of chemical, they obtained the equivalent of 40 milligrams of quinine, which is about a twelfth of a dose. The cost of quinine as produced by the two men in the laboratory would run to many thousands of dollars per dose.

Business of Engineers

But it is the business of chemical engineers, not research men, to take these discoveries and find way of translating costly laboratory methods into large-scale production plans. Chemical engineers are optimistic these days, and with reason. They took 100-octane gasoline which cost a thousand dollars a gallon in the laboratory, and found ways of making it in vast quantities, and cheaply. They are the men who took the new vitamins and a dozen other drugs and found ways to make them cheaply in bulk.

The trail which the Polaroid men blazed is rocky and winding, but already there are indications that further work may smooth it down and provide short-cuts. For instance, the quinotoxine which they found at the end of the road is a mixture of two varieties, one of which had to be thrown away to make quinine identical with the natural product. The discarded molecule is a "left-handed isomer" of the other, that is, it looks like a mirror reflection of the one which is used, and it does not exist in nature. Plans are under way to test this new molecule on malarial birds and monkeys, and it may turn out to be just as good, or better, than the right-handed one which yields real quinine. If it does, there will be no need to separate the two. This would not only simplify the process, but would more than triple the yield. Cost, of course, would be correspondingly cut.

Another Scarce Drug

After they had reached their goal, Woodward and Doering suddenly realized the importance of the fact that they had also produced quinidine—a drug important in the treatment of heart ailments—which is now so scarce that not even the armed services have enough of it, and its civilian use is rationed on a strictly life-or-death basis. Quinidine is now derived from natural quinine by a slow and expensive process. If the Woodward-Doering discovery is successfully put into commercial production, synthetic quinidine may turn out to be of even greater wartime value than man-made quinine itself.

There are other exciting possibilities. A number of related drugs of unknown medical value were created in the process of constructing the quinine molecule. Nobody knows what these young men have started in addition to creating quinine.

Since that morning when the weary partners capped their long grind with a "Q.E.D.," government agencies and drug-manufacturing firms have been in a turmoil of investigation and plan-making. The Polaroid Corporation, which instigated the work and paid for it, owns the new process, but President Land and everyone connected with the discovery is aware of the obvious fact that it must be developed in the public interest. The world has learned its lesson in allowing the Dutch quinine monopoly to control the price and production of a drug desperately needed by hundreds of millions of people. Land proposes to give non-exclusive licenses to whatever pharmaceutical firms are indicated by government authorities, and to use the income from these licenses to back further ventures in general research.

Meanwhile Woodward and Doering are plotting routes for further prospecting trips in atomic regions where man has never trod. Only scientists know the hazards they will face. They and their fellow chemists are a bit irritated at the question people have been asking, "Why wasn't quinine synthesized before?"

"Well, why wasn't it?" I asked, to see what would happen.

"It's like this," one chemist explained with weary patience. "There are 52 atoms in the quinine molecule, and there are 52 cards in a deck. Everybody uses the same kind of deck; why can't everybody win at cards?"

Doering made it shorter.

"Because no one ever came along as smart as Bob Woodward," he said.

This background story on the synthesis of quinine will appear in Reader's Digest for July. See SNL May 13 for earlier story and photograph.

Science News Letter, June 10, 1944

GETS THERE—This little plane can land on a small clearing in the jungle, or on a small landing strip along a road, to pick up a man wounded in combat. In this U. S. Army Air Forces photograph it is shown being pushed back out of the enemy's sight until it is ready to take off again.

CHEMISTRY

OEI Governs Molecules

Structure of giant synthetic rubber molecules is controlled by action of a new chemical agent. Makes possible uniform quality.

➤ A NEW CHEMICAL AGENT, extracted from a natural vegetable oil, controls the growth and structure of giant molecules which, in turn, determine the properties of finished synthetic rubber.

Facts about the chemical agent, developed by the United States Rubber Company, show that its use assures a standardized mixture of synthetic rubber at all times and permits the manufacture of completed tires, tubes, and other articles of war of known uniform quality.

Added to a mixture of butadiene and styrene, essential ingredients in the manufacture of GR-S synthetic rubber, this chemical agent controls the length of the molecular chains that determine the elasticity and strength of the product.

Too much of the chemical agent added to the mixture keeps the molecules too small, thereby producing a rubber that is soupy and of no practical use. Too little added to the mixture allows the molecules to become too large, making the rubber too stiff. Proper amounts of the chemical agent added to the mixture produces chains of molecules of optimum size and length, and the resulting rubber is of the desired consistency.

The exact chemical composition of the new chemical agent is one of the big secrets of the wartime synthetic rubber program. In speaking of it, chemists refer to it as O E I, "One Essential Ingredient," or by other specially coined terms.

The OEI chemical agent is being used today in practically all manufacture of Buna S synthetics. In order to meet the increasing demand for it by rubber producers, five major industrial chemical companies are manufacturing and experimenting with the chemical agent and substitutes.

Science News Letter, June 10, 1944

AERONAUTICS-MEDICINE

Grasshopper Planes Used To Evacuate Wounded

➤ THE TINY grasshopper planes, or flying jeeps, are being used by the Army in the jungles of Burma for air ambulance work.

Up to the present time these planes