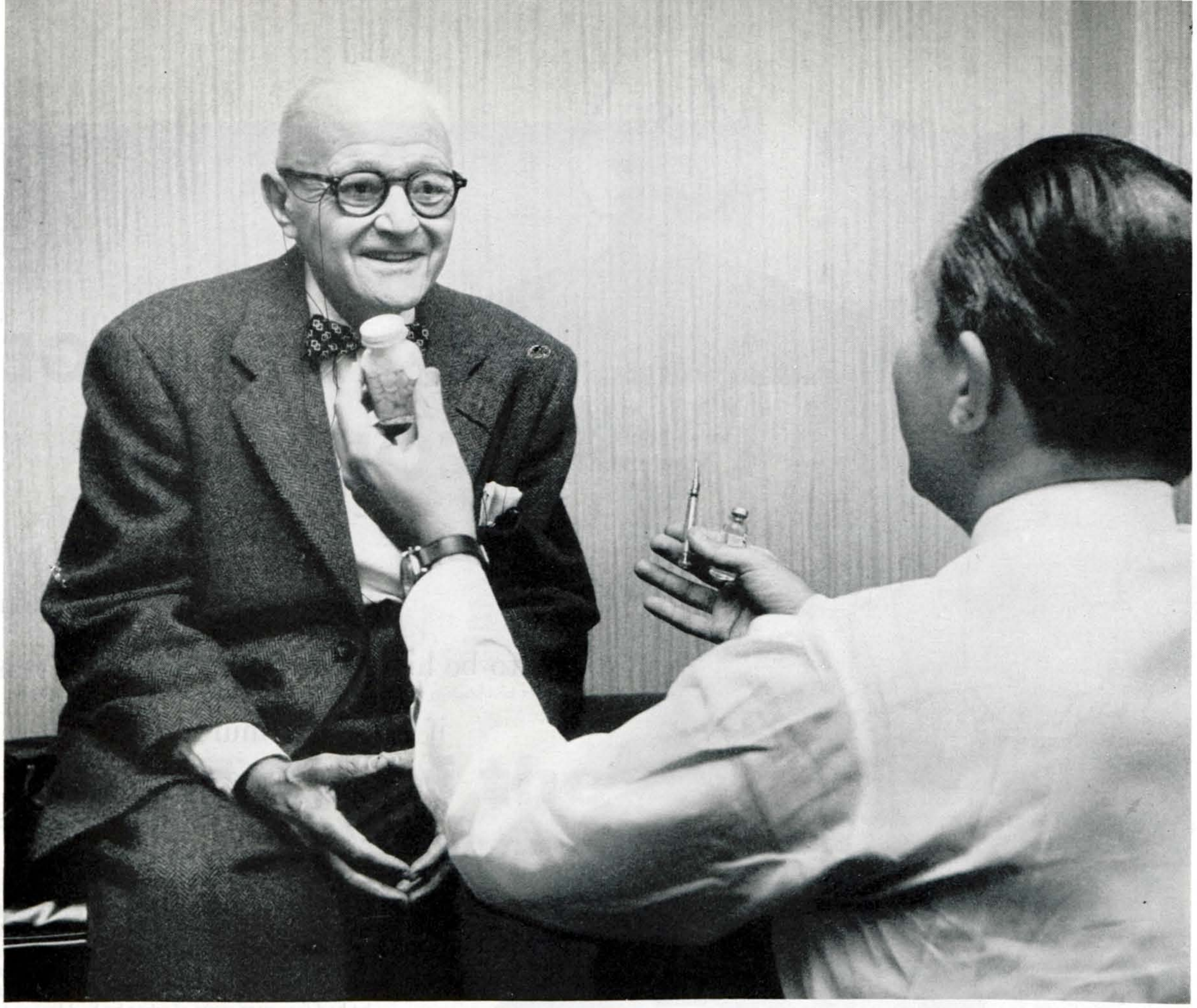


Good-by needle: Siegfried Fleischer, 79, has given himself 10,000 injections of insulin in his 55 years as a diabetic. Now he can use a new drug, tolbutamide, in pill form.

GOOD NEWS FOR DIABETICS

Dr. Auguste Loubatières. His long-overlooked research in sulfa drugs ultimately gave rise to the new pill.

Now, a new pill may free thousands of diabetics from their lifelong slavery to the hypodermic needle.

By Milton Silverman

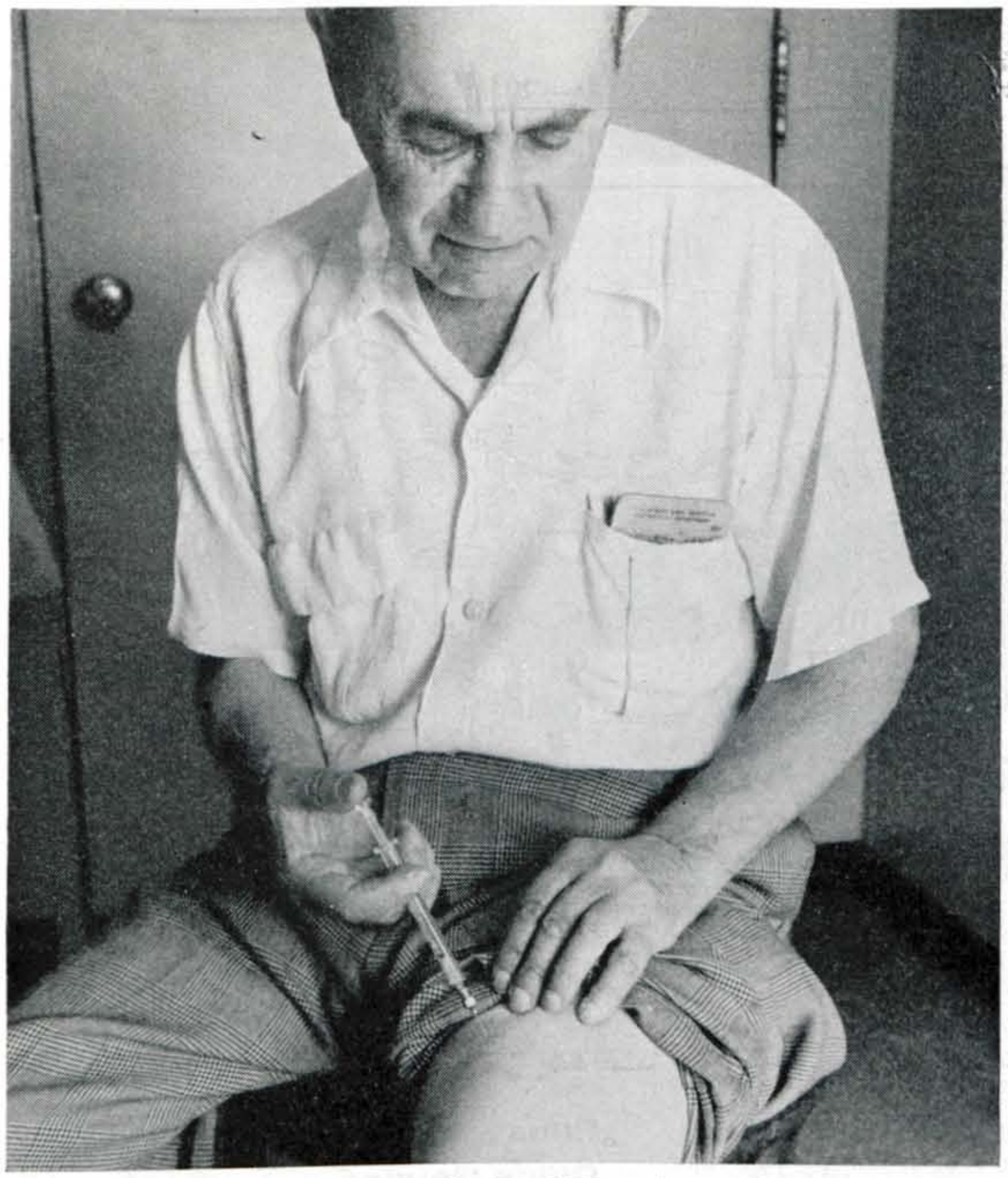
In the year 1902, a plump, successful young German building contractor named Siegfried Fleischer called upon a physician in Berlin and described his mild but annoying symptoms.

"So," remarked the doctor. "We will therefore make a few tests."

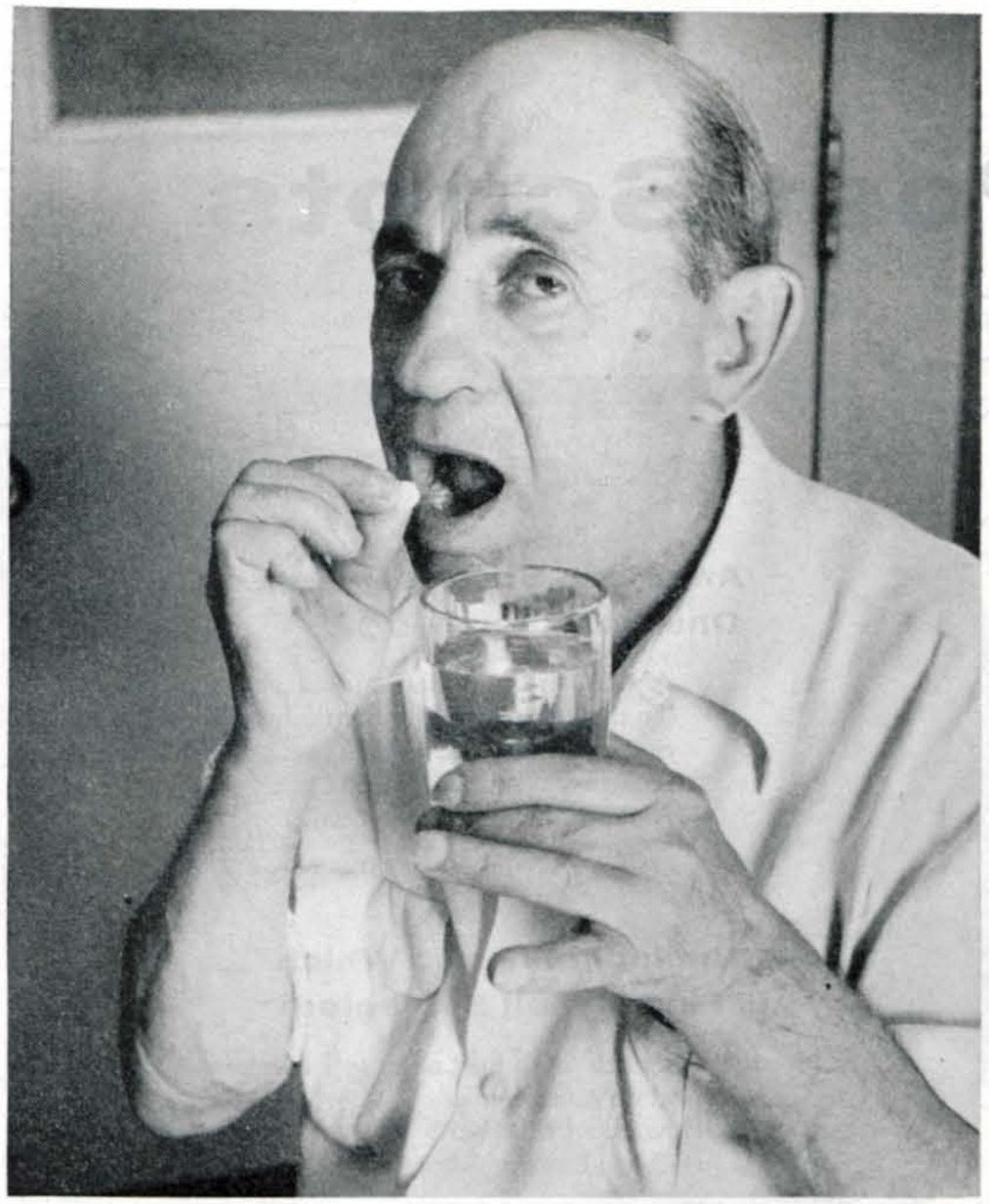
Within an hour, the tests were completed and the diagnosis was obvious. "Herr Fleischer," said the doctor, "I regret to inform you that you have diabetes."

In those days, more than half a century ago, medical men knew little about diabetes except that it was concerned somehow with the pancreas gland, it produced strange symptoms in many parts of the body, it was marked by high concentrations of sugar in the blood and by the presence of sugar in the urine, and it could not be cured or controlled by any known medicine. The only accepted treatment—more acceptable to doctors than to their patients—was a strictly limited diet essentially free from sugars and starches.

Young Fleischer was put on this kind of semistarvation menu. It took eighty pounds off



Diabetic Isadore Rosen injects insulin into his leg. An overdose might put him into the dangerous insulin shock, or an underdose might result in a diabetic coma.



No more hypodermics for Rosen. Tolbutamide (the Upjohn trade name is Orinase) works best on older patients who are affected with mild diabetes.

his weight, it barred him from most of the foods he once enjoyed, but it kept him alive.

After insulin was discovered, he was started on daily injections of this hormone, and continued these treatments for approximately thirty years. During this period, he gave himself about 10,000 insulin injections.

"I was grateful to have insulin," he said. "I no longer was forced to live on that terrible diet. I could eat a few things I liked—once in a while a piece of cake or a cookie. But insulin was a nuisance."

Ten thousand times Fleischer had to sterilize his needle and syringe. Ten thousand times he had to disinfect the skin on his thigh, insert the needle, and inject the potent solution. And day after day he had to carry his emergency ration of sugar in case his insulin overreacted. Never was he free from the fear that an overdose of insulin might put him into the dangerous insulin shock, or an underdose might be followed by the equally dangerous diabetic coma.

In 1938 he came to America with his wife and put himself under the care of a New York diabetes specialist.

"Even with the patient's scrupulous cooperation," this doctor said, "we could never quite keep his diabetes under complete control. His blood sugar was always on the high side, and he constantly spilled out a little sugar in his urine."

Finally, one day in 1956, the doctor called him into his office for a momentous conference.

"Mr. Fleischer," he said, "I have just received a new kind of medicine for the treatment of diabetes. I think you can take it instead of insulin. You can take it by mouth."

Fleischer was incredulous. "By mouth?" he repeated. "You mean no more injections? I won't have to take any more shots?"

"That's right," said the doctor. "Of course, it may not help you, but are you willing to take a chance?"

"For fifty years, I have been dreaming of this day—a medicine I can take by mouth! Naturally I will be willing."

The new drug was called tolbutamide, or Orinase. It was prepared in the form of white tablets with a faintly bitter taste. Fleischer was directed to swallow four tablets a day for the first week, and then two tablets a day thereafter—presumably for the rest of his life.

"Within a week," the doctor reported later, "the patient's blood-sugar levels were down to normal and, apparently for the first time in many years, his urine tests were negative. Under continuing treatment, his diabetes has remained under control."

This year, after more than eighteen months on tolbutamide treatment—and with no more insulin injections—Fleischer was still "under control." His blood tests were still satisfactory, and his urine tests were negative. At the age of seventy-nine, white-haired, courtly, punctilious in his manners, he was still a diabetic—but he was exceedingly happy.

"In my whole life," he said, "I have never been so relaxed."

Siegfried Fleischer, who had gone through the whole range of so-called modern diabetes therapy during his lifetime, was among the first patients in the United States to be put on tolbutamide treatment. By this spring it was reported by one pharmaceutical company—the Upjohn Company, of Kalamazoo, Michigan—that the new oral antidiabetic was being used experimentally by more than 15,000 patients in this country and 30,000 in Europe.

Tolbutamide was described repeatedly and emphatically (Continued on Page 46)

Dr. Henry Dolger, of New York's Mt. Sinai Hospital, treats a diabetic expectant mother with Orinase.

Dr. C. J. O'Donovan, of the Upjohn Company, examines some of the case histories required by U.S. authorities before approving release of the drug.

Good News for Diabetics (Continued from Page 39)

as no true substitute for insulin. It is not the long-sought "oral insulin." It is a different chemical with a different action, and its role appears to be limited primarily to victims of mild diabetes—those who produce a little insulin but not quite enough for their own needs. These potential users may include as many as 1,400,000 of the 2,000,000 diabetics in this country.

Even by this June, when tolbutamide was finally approved by the Food and Drug Administration for general use by the medical profession, there was no complete agreement on its significance. In some quarters it was hailed as the greatest boon to diabetics since the discovery of insulin. On the other hand, some experts vigorously continued to dispute such assertions; they insisted that tolbutamide must still be regarded as an experimental drug, its long-term effects are still unknown, and its role in practical medicine remains to be accurately charted.

"The clinician will not be entirely at ease in the use of these compounds until the exact mechanism of their function is known and proved to be innocent over long periods," said Dr. Garfield G. Duncan, of Jefferson Medical College, Philadelphia, in a recent review of tolbutamide and related drugs. "However," he added, "with growing experience with these products, the favorable indications increase."

Behind the development of tolbutamide and its chemical relatives lies a record of tragic errors, tests on hundreds of proposed remedies, and a most fortunate medical accident—an accident which had to occur twice before its meaning became apparent. According to medical historians, this is what might well have been expected, for the whole study of diabetes has been marked by accidental discoveries.

In 1796, Dr. John Rollo, surgeon general of the British Royal Artillery, stumbled upon the dietary treatment of the disease. "The diet," as he put it, was "to consist of animal foods principally."

Then, in 1920, Dr. Moses Barron, of the University of Minnesota, accidentally discovered that a certain blockade of the pancreatic ducts would destroy one portion of the pancreas but spare another part—a part which turned out to be the source of insulin. In 1921, Drs. Frederick Banting and Charles Best, working at the University of Toronto, picked up this clue and followed it to isolate insulin. For their epochal discovery, the two Canadians and their colleagues shared in the award of the Nobel prize.

Insulin was truly magnificent for millions of patients. It spared them from terribly rigorous diets, from increasing weakness and even from early death. But insulin treatment was far from perfect. It failed to help some patients. It had to be given with considerable care and according to exact dosages. And, since insulin itself is destroyed in the digestive tract, it had to be given by injection.

Accordingly, many investigators undertook a search for other remedies, especially for remedies which could be taken by mouth. They tried onion juice, microbes from the intestines of doves, and extracts of yeast, mushrooms, whortleberry leaves and carrots. They tried highly recommended native "cures" from Greece, North Borneo and the jungles of Africa. All of these proposed agents were either ineffective or too deadly for human use.

In the 1920's, a group of German chemists announced what they claimed was a safe, orally effective antidiabetic chemical known as Synthalin. It may have been effective, but it was certainly not safe. Put on the market too rapidly, before adequate testing could be completed, Synthalin produced serious liver damage in 40 to 50 per cent of patients who tried it.

Then came the first real break. During World War II, a team of chemists prepared a new microbe killer, a sulfa drug listed under the code name of 2254-RP. Early in 1942 it was sent for clinical trials in Southern France to Dr. Marcel Janbon at the Montpellier Clinic for Contagious Diseases.

"We suggest," said the chemists, "that this new compound be tested in the treatment of typhoid fever. It should be administered by mouth."

Although France had already fallen, the Germans had not yet moved occupation troops into Montpellier. Nevertheless, conditions were unhappy. Food supplies were running short, malnutrition was common, sanitation was poor, and there were plenty of patients suffering from typhoid. Doctor Janbon selected several of these victims for the test and proceeded to give them the new pills.

The results were fantastic. Some patients seemed to benefit from the new sulfa drug. Others, however, soon developed strange and shocking symptoms. They became dizzy and faint, they shook and trembled, and they perspired heavily. Two of these unfortunate people—a nineteen-year-old girl and a thirty-one-year-old woman—died in a few days.

Doctor Janbon hurried to the nearby physiology laboratories at the University of Montpellier and consulted his brilliant colleague, twenty-nine-year-old Dr. Auguste Loubatières.

"What could have happened?" he asked.

"Well," said the physiologist, "the symptoms you describe in your patients are precisely the same as the symptoms I can produce in my dogs if I give them too much insulin. It appears that your new sulfa drug lowers the sugar concentration in the blood."

"Impossible!" said Doctor Janbon.

"Very well," said Doctor Loubatières, "we shall prove it."

Immediately the scientist began animal experiments in his laboratory. "On June 13, 1942," he reported later, "we were able to assure Doctor Janbon that the oral administration of 2254-RP produces a prolonged lowering of the blood-sugar level."

Two weeks later, Loubatières made the significant discovery that the new chemical had this remarkable action only if some insulin was present in the body. It worked if the pancreas was intact, or even if a large portion of the gland was removed. But if the entire pancreas was cut out, and no insulin was being produced, the sulfa drug was ineffective.

It soon became evident that although 2254-RP itself was too fleeting in its action and not suitable for use in human beings, a longer-lasting and safer sulfa derivative might be found to treat diabetics—an orally effective drug for those patients whose disease stemmed from a "sluggish" pancreas or insufficient insulin production. Here was the first lead to a safe pill for diabetics.

Incredibly, practically no one seemed interested. The French scientist himself performed animal tests on about a dozen other new sulfa drugs, but none was entirely satisfactory. He published numerous articles, and he gave many lectures. But except for a few other workers in France, Germany and the United States, who made a few preliminary but fruitless investigations, Doctor Loubatières' work was generally overlooked, ignored or ridiculed.

"We knew about his research for more than ten years," one American drug-company official admitted at a recent conference. "Until my dying day I shall continue to wonder why we didn't pick it up."

In February, 1954, almost twelve years after the accidental discovery in the typhoid-fever wards at Montpellier, essentially the same accident occurred in Berlin. This time the chemical was a new, long-lasting sulfa drug, later called BZ-55, created by the German firm of C. F. Boehringer and Sons. It was turned over to Dr. Hans Franke, of the Augusta-Viktoria Hospital, who then turned it over to his young assistant, Dr. Karl Joachim Fuchs, for routine tests as a germ killer.

"Oh, good, you gave junior his bath."

THE SATURDAY EVENING POST

In 1954, much of the glamour had gone from the sulfas. Penicillin and the other antibiotics were available, and testing new sulfa drugs was considered a thoroughly unexciting chore. Nevertheless, Doctor Fuchs proceeded with his routine assignment in routine fashion, administering BZ-55 to patients hot and feverish with pneumonia, kidney infections and similar ailments.

"The therapeutic effect was as anticipated," he reported. "There was a prompt return of the temperature to normal."

Then he suddenly spotted a few patients who were not reacting as anticipated. They were dizzy, shaking and perspiring. They were acting as if they had been given an overdose of insulin.

"I think I should try this on myself," said Doctor Fuchs.

Two hours after the young physician swallowed the tablets of BZ-55, he became faint, trembled and perspired, and announced that he felt tired and hungry. At the same time, tests showed that his blood-sugar level had dropped far below normal. It stayed down for nearly six hours, and then slowly came back to the proper level while his shaking and perspiring ceased.

"Now what?" he asked.

"Now we will repeat this several times," said his chief. "If we get the same results, perhaps we should find some patients with diabetes."

When diabetic patients were taken off their insulin injections and given the tablets of BZ-55 instead, the new sulfa drug proved to be remarkably effective. Slowly, over several days, it brought elevated blood-sugar concentrations down to normal, kept sugar from pouring out in urine, and it made the patients happy.

In October of 1955, after months of cautious tests, the Berlin physicians made their first formal report. They had treated more than fifty patients, following some of them for more than a year.

"In reviewing our entire patient series," they said, "we are inclined to believe that this effect is seen in 80 per cent of all diabetics, especially in light to moderate diabetes, regardless of how long the disease has existed. . . . Toxic side effects, for which we have kept a continuous and close watch for over a year, have not been observed so far. . . . We recommend the clinical use of BZ-55 on as large a scale as possible."

At the same time, Dr. Ferdinand Bertram and his associates in the Barmbek General Hospital at Hamburg reported essentially the same results with a group of eighty-two patients. The new drug, they said, failed to help young patients and those afflicted with severe forms of the disease.

"In contrast to this, astonishing therapeutic results were obtained in older diabetics," they stated. "In some cases, the treatment was amazingly successful. BZ-55 is the first antidiabetic substance whose effectiveness following oral administration has been proven beyond doubt."

The results seemed too good to be believed. In the United States, by and large, these results were not believed. The tragic case of Synthalin, with its toxic side effects, was still clearly remembered here. Accordingly, American physicians greeted the first news of BZ-55 with skepticism and grim warnings.

This go-slow attitude was endorsed thoroughly by officials of Eli Lilly and Company, of Indianapolis, who had brought BZ-55 to this country for experimental purposes. "It must be used with caution," they said, "and particular attention must be paid to possible toxicity resulting from long-term administration."

Last October, after painstaking investigation on human (Continued on Page 50)

(*Continued from Page 46*) volunteers, it was obvious that the doubts and warnings had been justified. American diabetes experts agreed with the German claims that BZ-55 was highly effective, but they could not agree with the German claims that it was highly safe.

"Forty thousand patients in Germany have taken this drug without any serious side effects being reported by German investigators," Dr. Kenneth Kohlstaedt, of Eli Lilly claimed, but he added that this had not been the experience in the United States.

The trial on thousands of patients in this country revealed that significant toxic side effects had occurred in about 5 per cent of the subjects, and in one institution—the famed Joslin Clinic, in Boston—side effects were noted in about 9 per cent. Eight or nine deaths had been charged to the drug in the nationwide test.

"We deeply regret that this compound apparently does not meet the rigid requirements for a drug that must be taken throughout life," said Doctor Kohlstaedt in announcing the end of the BZ-55 trials. And he added, "We share the disappointment of many diabetics."

Interestingly, American doctors learned later, BZ-55 was not withdrawn by the German manufacturers, and even as late as this spring was still being used by tens of thousands of patients in Europe.

But while BZ-55 was being shelved in America, another and curious oral antidiabetic was rapidly moving forward. Synthesized by chemists at the Hoechst Dyestuff laboratories in Germany, it was not a true sulfa drug, although it was a distant chemical cousin. Technically, it was called a sulfonyl-urea compound. This is the drug now being used under the name of tolbutamide, and introduced in the United States by the Upjohn Company under the trade name of Orinase.

"It is a strange compound," said Dr. C. J. O'Donovan, of Upjohn. "It has none of the germ-killing properties of the true sulfa drugs. Also, it seems to have none of the toxic properties of some of the sulfas. All it appears to do is help a lot of diabetics."

German investigators were the first to try tolbutamide, and groups of doctors in Augsburg, Frankfurt, Freiburg, Karlsburg and Munich had reported tests on 781 diabetics, with excellent results in more than half. "The untoward effects are remarkably slight," said the German physicians.

The Upjohn scientists, with admirable caution, decided to check for themselves. They tried the new chemical on dogs, rats, toads, rabbits, ducks and chickens.

In November, 1955, what were termed "preliminary preliminary trials" were begun at the University of Pittsburgh, Western Reserve University, the University of Washington, Chicago's Michael Reese Hospital, the University of Illinois, Peter Bent Brigham Hospital, in Boston, and a few other medical centers.

"These were cautious, short-term studies," it was reported. "Only a few hundred patients were involved. We were sure that tolbutamide would work. What we wanted to know, with our fingers crossed, was whether it would work safely."

In three months, no serious side effects were noted. The "preliminary preliminary" trials were ended, and the "preliminary" field test was begun. This was a broader study, destined to include many thousands of patients, but the attitude was still one of skepticism and watchful waiting. Again, the scientists were confident that the drug would work. But would it work safely?

"It was a harrowing time," said one Upjohn worker. "Sooner or later, I felt, the whole thing would blow up—I'd go to my office some morning, and there would be a telegram reporting the first serious side reactions."

All during 1956, experts continued to issue warnings and urge caution. Doctor Best, in Toronto, speaking mainly about BZ-55, stated that "while the work is of high significance, results may dash the hopes of those longing for an agent to free them from the tyranny of the insulin syringe."

Editors of The Journal of the American Medical Association wrote, "It behooves all physicians concerned in the treatment of diabetic patients to watch the results of forthcoming study. . . . The drugs at present are not available for sale, and their introduction into general use should come only after exhaustive trials, more definitive knowledge of the mechanism of action, and, especially, long-term observation for any possible chronic deleterious effects."

The American Diabetes Association spoke out against any premature optimism that the new chemicals would soon replace insulin injections.

Meanwhile investigators began publishing their findings on tolbutamide in the medical journals. Their reports did not instantly banish all opposition, but they served to diminish it. The successful treatment of thirty-four out of forty-four patients was described by Dr. Arthur Mirsky and his associates at the University of Pittsburgh; three out of five patients by Dr. Laurance Kinsell and his colleagues at the Highland-Alameda County Hospital in Oakland, California; fifty-eight out of seventy-five by Dr. Sol Sherry at Washington University, St. Louis; and 109 out of 143 by Dr. Samuel J. N. Sugar, of the District of Columbia General Hospital. One of Doctor Sugar's patients was a young mother who was safely carried through her pregnancy with tolbutamide, and who gave birth at the appropriate time to a healthy eleven-pound boy, while two others in the same group were maintained on the new drug while they successfully underwent major surgery. Both pregnancy and major surgery are generally believed to be particularly dangerous in diabetics.

At the University of Toronto, long considered the veritable shrine of insulin research, Dr. W. T. W. Clarke reported that twenty-five out of forty patients were apparently under control with the new chemical.

One of the largest groups tested with tolbutamide was studied by Dr. Henry Dolger, head of the diabetes clinic at New York's Mt. Sinai Hospital. "The general impression on more than seven hundred patients," he told the New York Academy of Sciences last February, "indicates that tolbutamide can be used successfully in the treatment of seventy per cent of all adult patients. Toxic effects, affecting less than one per cent of the group, consisted mostly of transient skin reactions."

Roughly one half of the New York diabetics had previously been attempting to control their disease by diet alone, but without noticeable success. The other half had been taking insulin before changing over to tolbutamide.

"Among diabetics over the age of forty," Doctor Dolger told his fellow physicians, "tolbutamide will be successful in four out of five patients. Among those twenty to forty years of age, it will be successful in one out of three."

The New York investigator, like other workers, noted that the oral drug rarely worked in what is termed "juvenile" or "brittle" diabetes. This form seems to be almost a different disease, often marked by very high but erratic insulin requirements, and by frequent and serious complications.

Very recent reports reveal that a few juvenile patients have been helped by a third new compound, a synthetic imidourea preparation known as DBI, although the drug, tested in New York and Boston, has caused nausea and vomiting in several cases.

At the Joslin Clinic, in Boston's Deaconess Hospital, where the earlier tests on BZ-55 had resulted in two deaths and in toxic side effects in 9 per cent of the patients, Dr. Alexander Marble and his colleagues reported that tolbutamide had been used, with no deaths, and with undesired but minor side effects—mostly skin rashes—in only nine tenths of 1 per cent.

After a year's trial, involving 420 patients, Doctor Marble confirmed the original reports from Germany that the new compound can lower blood sugar in the majority of middle-aged and elderly diabetics. "Judged by strict criteria," he said, "sixty-four per cent of selected patients on tolbutamide achieved good or fair control of sugar in the blood and urine."

The best results, he added, were obtained with older patients afflicted with so-called stable diabetes, requiring not more than forty units of insulin daily. He emphasized that the new drug should not be tried in the presence of diabetic coma or other complications, acute infection, liver or kidney disease, or a known sensitivity to any of the sulfa drugs.

By last June, the Upjohn scientists in Kalamazoo—along with physicians all over the country—were evidently breathing easier. The earlier controversy, which had flared originally over BZ-55, but later involved tolbutamide, was continuing, and would undoubtedly continue indefinitely in some quarters, but most of the heat was gone. The Upjohn men had compiled detailed information on 7147 patients treated by some 400 different doctors. Approximately 7000 were in the twenty-one-to-eighty-year age group, and about 76 per cent of these subjects had given what were termed "good" or "excellent" responses.

Although there had been the expected deaths from pneumonia, cancer, heart attacks and even suicide which naturally occur in this age group, there had been no death considered directly attributable to the drug. About 3 per cent of the group had shown some side reactions—mostly a temporary case of hives or other skin rash, indigestion, nausea, or a "sweet" or "metallic" taste sensation—but no serious toxic effects were reported. During the test period, more than 120 patients had each consumed more than a pound of the tablets.

There was still considerable controversy over the precise mechanism of tolbutamide in the body. "Our understanding of its mode of action," one expert confessed, "is in a state of crystallized confusion." Evidence was accumulating, however, to suggest that the remarkable chemical acts at least in part by stimulating release of insulin from the pancreas and decreasing release of sugar from the liver. It cannot work unless at least some insulin is present. It clearly cannot "cure" diabetes, but must be taken indefinitely. Dietary control is still essential.

"The use of tolbutamide does not give license for dietary abuse," it was emphasized.

Similarly, there was still no general agreement on the best way to select those patients most likely to be helped by the new tablets, or how to make the switch from insulin injections to tolbutamide tablets—whether by an all-at-once routine or by a tapering-off process—with maximum efficiency and safety. After about two years of trials, there was no way to predict whether or not a patient might continue to benefit from the tablets for periods of five, ten or twenty years.

"Nevertheless," says Doctor O'Donovan, of Upjohn, "with the advent of these new chemicals, we may be upon the threshold of a new era of therapy in diabetes, for they give promise that a significant portion of our diabetic population may be unshackled from syringe and needle. . . . There is an attitude of cautious enthusiasm." THE END

"I'll wait for you, Dudley, even if I have to date someone different every night to keep from getting serious about any one fellow."

THE SATURDAY EVENING POST