GOOD NEWS FOR DIABETICS

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...
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 con­
tinued these treatments for approximately
thirty years. During this period, he gave him­
self 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 steri­
zate 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 over­
dose of insulin might put him into the danger­
ous insulin shock, or an underdose might be fol­
lowed by the equally dangerous

in a diabetic coma.

"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
tables with a faintly bitter taste. Fleischer was
directed to swallow four tablets a day for the
first week, and then two tablets a day there­
after—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. Un­
der 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 satisfac­
tory, 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, Michi­
gan—that the new oral antidiabetic was being
used experimentally by more than 15,000 pa­
ients in this country and 30,000 in Europe.

Tolbutamide was described repeatedly and
emphatically (Continued on Page 96)
equate 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, some chemists prepared a new microbe killer, a sulfa drug registered under the code name of 2254-RP. Early in 1942 it was sent for clinical trials in Northern France by 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 and were still using sulfa drugs, as a substitute for insulin. On the other hand, some experts were convinced that the exact mechanism of their function is known and proved to be innocent over long periods of treatment. Dr. H. B. S. can, of Jefferson Medical College, Philadelphia, in a recent review of tolbutamide and related drugs, “However,” he added, “with growing experience we have observed indications that the sulfa drugs may be dangerous.”

Behind the development of tolbutamide and its chemical relatives lies a record of tragic errors, tests on hundreds of people, and a repeated occurrence of medical accident—an accident which had to occur twice before its meaning became apparent. According to medical historians, the policy of the medical profession has been to suppress fully all records of similar accidents. This is the result of a great belief in the”的正确性。
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 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 behoves all physicians concerned in the treatment of diabetic patients to watch the results of forthcoming study... The drugs are not present or 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 ban his opposition, but he continued to urge caution. The successful treatment of thirty-four out of forty-four patients was described by Dr. Arthur Minsky 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. Sui 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 woman 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. F. 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 having been used in the United States by the Upjohn Company under the trademark 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, in so far as it may have none of the toxic properties of some of the sulfa drugs. 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, Karlsruhe, 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 American Diabetic Association, 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, designed to include 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, this is the drug now being used under the true sulfadiazine drug. Also, it seems to have effectively treated many diabetics, with excellent results in the treatment of many diabetics."

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