Dr. Charles Best:

The Battle of the Beta Cells

To insulin's co-discoverer, the causes of diabetes remain a major concern

SCHOLAR and researcher Best says his ideas about diabetes are still changing.

Every Christmas, a Toronto physician who conducted the first clinical trials with insulin receives a letter from a former patient, reminding him of the year 1922. For that diabetic and thousands of others, it marked the beginning of a new life.

For physicians, it was also the beginning of a new era of thinking about the disease. Dr. Charles Herbert Best, co-discoverer of insulin in 1921, looks on it as a kind of Forty Years' War, during which "the battle of the beta cells" has raged — both within the diabetic patient and among those who try to understand the disease.

Dr. Best still considers the conflict of forces and ideas "a fascinating engagement." This year, bringing his theories of diabetes up to date, he says:

"When we were ignorant of the complexity of the situation, diabetes appeared to be a rather simple and straightforward disorder." All this has changed.

Even now, he says his ideas about diabetes are "pretty fluid." But for the moment, he believes there are eight possible causes:

(1) Defects in the pancreas as a whole, including the beta cells (those cells of the islands of Langerhans responsible for secretion of insulin).

(2) Defects in insulin formation.

(3) Defects in insulin liberation.

(4) Abnormal destruction of endogenous insulin.

(5) Genetic defects involving insulin-dependent reactions.

(6) An excess of diabetogenic substances.

(7) Genetic defects making tissues abnormally susceptible to diabetogenic substances.

(8) Genetic defects independent of hormonal actions.

The primary abnormality, he adds, might be in the pituitary, adrenal cortex or medulla, thyroid, or alpha cells of the pancreas. On the other hand, it might be in the metabolic processes which are independent of hormonal actions. "There is quite a lot of support for the idea that the primary defect in some cases is not in the pancreas," Best says. "But this does not mean that in other cases it may not be there.

"If the beta cells react normally, you don't get diabetes, even if there is an excess of antagonists. The genetic lesion might be in the beta cells and the beta cells would then be in the fight

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from the beginning. Or they might be committed later in response to an excess of an antagonist.

"But whether primarily or secondarily, they are certainly in it. Diabetes, therefore, is fundamentally a battle in which the beta cells are involved."

Aside from these complexities, Dr. Best thinks that one basic question is whether the disease is caused by a primary lack of insulin or an excess of antagonist leading secondarily to insulin lack. Whichever it is, he is sure the disease could be traced back even further to a genetic defect.

A genetic lesion could, of course, be expressed in many ways. It might interfere with insulin synthesis by causing a lack of essential enzymes or by not providing enough energy. It might affect any or all of the membranes through which insulin has to pass before reaching the nearest capillary. It might cause lesions in the transport system on which insulin acts to permit entry of sugar and other substances into the cells. Or it might cause either excessive binding of insulin or a failure in the mechanism that normally liberates it from its bound form.

Regarding this binding theory, Dr. Best wrote recently:

"This is one of the many 'active foci' in the insulin field, and the rapid advances being made will certainly bring about radical changes in our views."

His interest in insulin and diabetes has never flagged, and has been "the continuous thread" running through the work of his institute. But he has also been responsible for the discovery of the enzyme histaminase and the dietary factor choline, and has done important work on heparin.

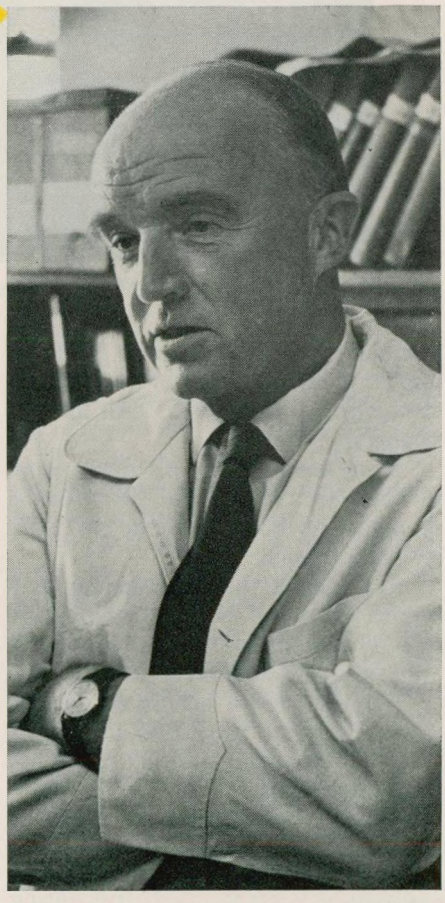
Best's researchers are now investigating a number of areas, including two that he considers "special." One is the study of the behavior of pure phospholipids, now available for the first time through the synthesizing skill of Dr. Erich Baer, head of the sub-department of synthetic chemistry at the University of Toronto. The other is experimental surgery. Also receiving much attention is an extension of Best's original heparin work and studies of atherosclerosis.

Best always tries to diversify his research investment. His early insulin work with Banting was strictly a gamble, in the sense that neither was paid for it and neither received any encouragement. The two of them occasionally toured the city bargaining for dogs with their owners, then paying for the animals out of their own pockets. At one point Best borrowed money from Banting, who got it by selling his automobile.

In those days, Dr. Best was a 22-year-old physiology and biochemistry student at the University of Toronto. Today, at 63, he is a leading figure in Canadian medical research — director of the Banting and Best Department of Medical Research and head of the department of physiology at the University of Toronto.

In his laboratories, Best believes that in addition to the methodical approach, there must be a certain amount of gambling as balm to the soul.

"Each investigator must concentrate his efforts on a main problem," he says, "but within this area there are always good opportunities to risk part of his time in a real adventure.



THOUGHTFUL frame of mind overtakes Best as he weighs his words and ideas.

"Undoubtedly most investigators do have such plans, but many of them, probably to protect themselves against disappointment, bury their dreams at various depths within themselves.

"When one has passed the threescore mark it is perhaps permissible to believe that the open discussion of one's hopes may encourage and stimulate younger investigators, at least as much as does the impersonal, coldly scientific presentation of advances in our knowledge.

"It is not, of course, suggested that the former procedure should ever interfere in any way with the latter," Dr. Best observed.

It would be difficult to tell that Best has "passed the threescore mark" by looking at him or watching him at his work. Rising at 5:00 or 5:30 a.m., he has coffee with his wife in their house overlooking Toronto, then does a day's writing before "going to work." Then he walks the three-mile stretch between home and lab. He is writing two or three books at the moment.

He travels extensively, is in Toronto only about six months of the year, and during the other six might be found almost anywhere else in the world. When at home, he likes to spend weekends in his stone house in Halton County, where he keeps three horses. A man with a look of quiet determination and strength, Best seems to be basically somewhat shy, despite his almost continuous exposure to the limelight. His hobbies are not gregarious ones — painting, riding and golf—and his colleagues say he enjoys nothing so much as reading a good scientific paper.

His family background is filled with a tradition of scholarship and public service. Best's Canadian-born father was a country doctor in West Pembroke, Maine. As a small boy Best often went with his father on country calls down muddy roads or across frozen fields. "Often, the doctor operated on his patients on the kitchen table, while a small yellow-haired boy seated at its head dropped ether onto a cone to keep the patient anesthetized," write Best's colleagues Wrenshall, Hetenyi and Feasby in *The Story of Insulin*.

Best's sons are also scholars. Henry

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BETA CELLS *Continued*

Bruce Macleod Best, 28, graduated in arts from the University of Toronto and obtained his M.A. in early Canadian history *magna cum laude.*

After finishing his Ph.D. examinations he served for a time as executive assistant to Canada's minister of external affairs.

Charles Alexander (Sandy) Best, 30, was elected to Canada's parliament at the age of 25. A nursery owner who grows prize-winning lilies, he lost out in the last election, but found time to finish a Ph.D. in botany, which was presented to him just a few days ago at the University of Toronto.

This fall has been full of celebrations for Dr. Charles Best. Early in

CALORIMETER used in the original insulin work is among prized possessions.

November, to celebrate the 40th anniversary of the publication of the first clinical paper on the isolation of insulin, most of an issue of the *Canadian Medical Association Journal* was given over to reminiscences of the discovery.

And the Toronto Academy of Medicine, where the first paper on insulin was presented outside of the university, gave bronze busts of Banting and Best to Lady Banting and Dr. Best.

Closing the program, Dr. William Boyd, author of pathology texts famous the world over, remarked that "the history of medicine is like the history of the world. It is the story of but a few people. Few men only leave their footprints in the sands of time, and if they would do so, they must wear their working shoes."

Charlie Best's footprints are there and he still wears his working shoes. He has not had them off since 1921. ■

LIVELY DEBATE OVER PREDIABETES

The discovery of insulin 40 years ago cast a sudden brilliant light on the understanding of diabetes, and produced the modern classic concept of the disease. Some experts now hint that perhaps the illumination was too bright; it may have blinded them to any other new ideas.

According to the new views, the disorder of carbohydrate metabolism does not break out suddenly following a static, quiescent period of prediabetes. Instead, prediabetes must now be considered as an active and dynamic state in the life of an apparently normal person who is genetically diabetic. Clinicians discussing the point at a recent New York Diabetes Association meeting showed remarkable unanimity of opinion. Some investigators even went beyond the general change in attitude and proposed startling new concepts:

▸ Clinically, the known complications of diabetes are not really products of the carbohydrate disorder. Hyperglycemia, as measured by the standard glucose tolerance test (GTT), and "degenerative changes" are different aspects of a genetically controlled process. These aspects develop independently of each other and at different rates.

A number of clinical possibilities thus arise in any group of randomly selected patients. Among the well-documented possibilities are abnormal GTT alone and abnormal GTT occurring before or about the same time as the degenerative changes.

But it is also possible for degenerative changes to occur long before the appearance of an abnormal GTT, or even without it. For example, Kimmelsteil-Wilson lesions, typical of advanced diabetic nephropathy, have been found in a patient whose GTT is normal at first but becomes abnormal after the administration of cortisone.

▸ The classic experimental model for studying diabetes may be the wrong one. Ever since the discovery of insulin, thousands upon thousands of animals have been made diabetic by depancreatizing them or administering alloxan to them. But the cause of insulin insufficiency in the majority of patients is not necessarily lack of pancreatic hormone, as shown by the pharmacodynamics of the oral hypoglycemic agents.

In his opening remarks to the meeting, Dr. Max Ellenberg, chairman of the association's clinical society, said:

"Since *all* the complications of diabetes may and do occur prior to any overt carbohydrate disorder, it seems clear that ' a prolonged period of poor control' is not a necessary prerequisite for their appearance. In fact, the very relationship to abnormal carbohydrate metabolism per se is subject to question, and considerable doubt is cast upon it."

To Dr. Ellenberg, the implication is clear that there must be factors other than insulin insufficiency operating. These must be effective prior to the clinical onset of diabetes.

While there was no unanimity of opinion on the definition of prediabetes, there was much agreement. Participants gave the most support to the definition published recently in an editorial in the *Journal of the American Diabetes Association,* signed by Drs. Jerome W. Conn and Stefan S. Fajans of the University of Michigan School of Medicine in Ann Arbor. Dr. Fajans expanded his views at the New York meeting.

The diabetes syndrome, in his opinion, comprises four stages. Three are asymptomatic; only the last — overt diabetes—is symptomatic.

The earliest of the four stages is prediabetes. "It exists from birth or conception until the diagnosis of diabetes can be established or suspected." A diagnosis of prediabetes itself can be made only in retrospect, Dr. Fajans said. He believes that during this stage, the diabetogenic forces are being successfully countered by compensatory mechanisms. As soon as these mechanisms fail and the diabetogenic forces begin taking over, producing signs of

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