THE ROMANCE OF INSULIN—*How a Young London Doctor, Reading a Medical Journal Struck the Idea Which Has Ended Centuries of Misery*

Canadian Brains and Canadian Perseverance Have Solved a Mystery Which Has Baffled the Scientists of the Civilized World and Cost Untold Pain and Suffering Among Mankind.

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In November, 1920, while reading an article in a periodical devoted to surgery, Dr. F. G. Banting, then an assistant in the physiology department of Western University, London, Ontario, conceived the experiment which finally resulted in the production of insulin. Thus culminated a series of medical researches, carried out through hundreds of years in an endeavor to control a disease—diabetes—which affects approximately one per cent of the population of the world, or in the United States more than a million persons.

The disease — diabetes — was described by Aretaeus, a Greek, who lived in the reign of the Emperor Hadrian in the second to third century A. D., in a classical description which can be improved on today only in its details of chemistry and physiology, sciences not so well known to the ancients.

What the Disease Does.

"The nature of the disease," he said, "is chronic and it takes a long period to form; but the patient is short lived if the constitution of the disease becomes completely established, for the melting is rapid, the death speedy. Moreover, life is disgusting and painful; thirst unquenchable, excessive drinking, which, however, is disproportionate to the larger quantity of fluid excreted; for more fluid is excreted; and one cannot stop them either from drinking or excreting fluid. Or, if for a time they abstain from drinking, their mouth becomes parched and their body dry; the organs seem as if scorched up; they are affected with nausea, restlessness and a burning thirst; and at no distant term they expire."

Aretaeus derived the term, diabetes, from the Greek term meaning siphon, although later philologists are inclined to give the term the meaning of "passing through," and it was believed that the essential feature of the disease was the rapid passing through the body of fluids.

However, credit is given to an English physician, Thomas Willis, for having discovered in 1674 that the fluid excreted is sweet in character, and a hundred years later other English physicians showed that this sweetness was due to its sugar content. From that time until 1889, few researches of importance were made on this disease, but in that year Mering and Minkowski, two foreign investigators, found that complete removal of the pancreas from a healthy dog would result in severe and fatal diabetes.

Pancreas is a Gland.

The pancreas is a gland which lies near to the stomach, the gallbladder and the upper part of the intestines. In stockyards and packing houses, it is commonly called "liver sweetbreads," thus distinguishing it from the true sweetbreads or thymus gland, which are commonly called "heart sweetbreads."

The sweetbreads, which the wily restaurateur serves appetizingly on toast under glass, are usually the pancreas of the sheep or hog, since these are small. The beef pancreas is a large organ, not so suitable for the palate of the gourmet.

As has been stated, the pancreas is a gland, and it has been the practice of investigators to determine the functions of glands by removing them from the bodies of animals and then observing the animals to see what changes might take place in their physical condition. When the foreign physiologists discovered the results which followed the removal of the pancreas, the most important step had been taken to determine the cause of a most fatal disease.

Now the article which young Banting was reading and which led him to his crucial experiment dealt with the relation of the islands or islets of Langerhans to diabetes. Students of microscopic anatomy had discovered that the pancreas is composed of two types of tissue, one of them a glandular tissue which secrets a digestive fluid known as trypsin, and the other characterised by the fact that its cells are distinct from the remainder of the pancreas. These are the islands of Langerhans, so called from the name of the investigator who first described them.

A Microscopic Romance.

After his description many earnest scientists endeavored to determine the function of these islands, and in 1886 an anatomist suggested that they have a secretion separate from that of the remaining portion of the pancreas. Since such a secretion was not found to come from the ducts or tubes which regularly conveyed the external secretion, trypsin, it would be known as an internal secretion. The latter term signifies that the secretion is poured by the pancreas into the blood stream, and is not poured directly into some cavity, as trypsin, for example, is poured into the intestine.

These experiments continued and it was discovered that the islets were the structures of chief importance in relation to diabetes. The manner of this discovery is fascinating from the standpoint of scientific detail.

For example, it rested on microscopic observation of portions of the pancreas taken from the bodies of persons who had died from this disease. It rested on experiments in which portions of the pancreas were removed from animals and the remainder subjected, after certain periods, to special study. In 1917, a Japanese, Kamimura, traced the changes in the tissue of the pancreas, after tying off its ducts, and found that the islets remained normal and that the animal would not excrete sugar in its fluid as long as these islets remained intact.

Test Power of Extracts.

Another method which the scientists use to determine the effects of any organ upon the body is to inject extracts of the organ into human beings and to determine whether or not such extracts produce undesirable changes. This is the basis of the use of a number of glandular preparations which have proved of immense value to the human being and, unfortunately, of the use of a number of other glandular preparations, the value of which rests only on the belief that since some are effective, these also may be of benefit.

For example, it is known that in the condition called cretinism, which produces idiots and dwarfs, there is a deficiency of the thyroid gland secretion. In this condition provision of the thyroid gland substance is beneficial in arresting progress of the disease and permitting normal development.

Many physicians attempted to treat diabetes by administering extracts of the pancreas to diabetic patients. However, the results were invariably of such character as to discourage the use of the product. In view of the fact that Banting has been successful in producing an extract which does yield satisfactory results, it may be well to credit those other pioneer investigators, Minkowski, Murlin, Kleiner and Zuelzer, for their pioneer attempts. In every case the experiments failed for reasons which today might not have obtained. The advance of science is a slow but steady process, increasing in rapidity as knowledge develops.

The Conclusive Experiment.

In the article which Banting was reading, there was a resume of the changes which occur in the tissues of the pancreas following the tying off of the ducts. As will be remembered the external secretion of the pancreas, trypsin, is a digestive fluid. When the ducts are tied off, this fluid is backed up into the gland and there results a degeneration in the glandular tissue of the organ. However, the islet tissue does not degenerate.

Since all of the previous experiments tended to show that the islet tissue is a significant factor in relation to diabetes, it occurred to Banting that this method could be utilized to obtain an extract which would consist almost wholly of islets. Obviously such an extract would be far more potent in its content of the active principle responsible for diabetes than would extracts of the entire gland.

Having elaborated this hypothesis, the next step of the investigator was to present it to Prof. J. J. R. Macleod, head of the physiological laboratory of the University of Toronto, who, in May, 1921, provided laboratory facilities and support in undertaking the experimental work.

Make Tests on Dogs.

The first experiment was, of course, to ligate the ducts of the pancreas in dogs and allow sufficient time to elapse for the degenerative changes to occur. The next step was to operate on other dogs, removing the pancreas and permitting development of diabetes. Then the first animals were painlessly chloroformed and the pancreatic tissue remaining following the degeneration hastily removed, sliced, ground in a mortar, extracted in salt solution and the mixture filtered. The fluid passing through the filter, having been raised to body temperature, was injected into the veins of the diabetic dogs. When a normal dog was injected with this extract there resulted a lowering in the percentage of sugar in the blood. When a diabetic dog was injected with this solution there was a lowering of the percentage of sugar in the blood and a lowering of the amount of sugar excreted in its fluids.

Hundreds Seeking Secret.

This, in brief, is an account of the first experiments on the production of insulin. The account does not, however, give any indication of the scientific methods employed or of the thoroughly accurate check on the work through the use of suitable controls, that is, the checking of every observation made on a normal animal. Furthermore, it gives but a poor account of the many researches of hundreds of physiologists, chemists and physicians all over the world who contributed their mites to the knowledge of this subject and who trembled repeatedly on the threshold of the final discovery without carrying the experiments to the final conclusion. It is almost romantic that it should have remained for Banting, as a result of an accidental observation made while casually reading an article outside the field to which he devoted himself, to see and to carry out the final step.

Preparation of the Extract.

As has been said, the previous experiments of many workers had shown that the external secretion of the pancreas, trypsin, or some other constituent, destroys the active principle of the internal secretion, presumably coming from the islets, when attempts are made to make extracts out of the whole gland.

Of course it would not be possible to prepare any considerable amount of an extract if the method followed in the first experiment had to be depended on for this purpose, i. e., operation on an animal, delay until degeneration occurs, and subsequent extracting of the glandular remainder after the animal has been killed. The Canadian investigators therefore decided to attempt some experiments with the pancreas of fetal or unborn calves.

This decision was based on some previous work by Professor Carlson of the Univeristy of Chicago, and a number of other physiologists, who had shown that the pancreas, in such animals, may be rich in the internal secretion and yet not subject to the destructive influences of the external secretion.

It was now found that extracts in salt solution of the pancreas of unborn calves in the fifth month of gestation, or intrauterine development, would have the same effects as did the degenerated pancrease prepared in the first experiment.

Life Lengthened Five-Fold.

A dog, from which the pancreas had been surgically removed, and which was therefore subject to diabetes, was kept alive with such an extract for seventy days whereas previously it had been shown by Dr. F. M. Allen, another investigator, that such a dog does not live beyond fourteen days.

It was now clear that a substance was present within the pancreas, quite certainly chiefly in the islet tissue of the pancreas, which, when injected, would supply some substance not present in diabetes, and which, therefore, was capable of sustaining life and adjusting the use of sugar by the body. The next step was to get this substance out of the pancreas of the adult animal. In the cow or ox the pancreas weighs about a pound, in the sheep or hog it is proportionately smaller, and slaughter houses in this country at least can supply liberal quantities of such tissues.

The researches of Banting and his co-worker Best, carried on under the guidance of Professor Macleod, were now still further extended with the assistance of Professor J. B. Collip, of the department of pathological chemistry in the University of Toronto.

Used Over and Over.

His chief contribution to the work was a method of extracting the ground pancreas, with alcohol, over and over again, thus circumventing the action of the trypsin and removing excess quantities of albuminous substances which form the basis of animal tissues and which may cause severe reactions when injected into the human body.

His efforts were successful, a suitable method was devised, and it was possible to deliver to the physicians who were to test the product on human beings, an extract practically free from proteins, from unnecessary minerals and salts, and capable of being injected without producing either severe symptoms at the point of injection or the previously described general reactions which follow the injection of albuminous or protein substances.

But there still remained to be determined a very important question: the matter of standardization and dosage. How important this really is will be seen in the following paragraph.

Dosage and Standardization.

The scientific physician of today, thoroughly trained in physiology and pharmacology, employs many potent drugs and remedies. How many persons who receive a life-saving dose of digitalis when suffering from diseases of the heart, of diphtheria antitoxin when strangling with the accumulation of membrane in the throat, or of thymol or oil of chenopodium when suffering with the lassitude and anaemia of hookworm infestation, stop to wonder how scientists arrive at the proper quantity of the remedy to be administered? And yet it is absolutely a matter of the person's life or death! To determine these things by trial and error on the human being would be a most uneconomical, inhumane, and as far as the test person was concerned, a perhaps uncomfortable process.

Already it has been shown how Banting and Best, utilizing dogs, were able to do experiments which ended in the isolation of a new remedy which will mean added life, health and comfort to millions on millions of human beings. In standardizing and assaying the remedy, and in measuring its potency, and thereby determining its dosage, it was possible to use smaller, less expensive and more readily available animals—a species known for its ability to reproduce with astonishing celerity—the rabbits.

What the Drug Does.

The distinguishing sign of diabetes is the presence of sugar in the excreted fluids. However, scientists have found that the amount of sugar in this fluid varies from time to time according to a number of variable factors. On the whole, however, it is quite definitely related to a much more constant measurement—the amount of sugar in the circulating blood.

The concentration of sugar in the blood of normal persons varies between 0.08 per cent and 0.12 per cent. In diabetes the concentration of the sugar content of the blood is definitely increased, ranging from 0.14 per cent to 0.5 per cent. Now, the primary effect of the extract made from the islets of the pancreas, and called insulin, from the word insula, meaning islands, is a reduction of the blood sugar.

When a rabbit which has gone without food for about sixteen hours is injected with a large dose of insulin, it becomes excitable, and later passes into a form of drowsiness, characterized as coma. Its breathing may be rapid, and its muscular excitability so intense, that clapping of the hands or stamping the floor will throw it into convulsive movements.

Standard Unit Worked Out.

In measuring the power of various preparations of insulin the preparation is injected into rabbits of definitely known weight, the percentage of blood sugar is determined at intervals after the injection, and the animal is watched for the appearance of the characteristic symptoms. It was determined that when the concentration of the blood sugar under the influence of insulin reaches 0.045 per cent, almost without fail the animals develop the characteristic symptoms. The amount of insulin which will produce such a state within four hours after injection is, for the present, called one unit, and we thus have a standard for calculating dosage.

However, the investigators did not yet discontinue their preliminary experiments, but studied many other factors of the body reactions in diabetes. They determined that when insulin is injected, the body is able to assimilate and dispose satisfactorily of increased quantity of sugars. They found that certain substances of a chemical character called "acetone bodies," the appearance of which in the excreted fluids of diabetics, when in considerable quantity, is a mark of danger, would lessen and disappear when insulin is administered.

Man Last In Tests.

It has been known that not only is the use of sugar by the body deranged during diabetes, but that the fats and proteins, other significant elements of foods, may be subject to unusual changes, and it was shown that insulin affects also the satisfactory utilization of fat. Again, scientific physiologists had shown that certain procedures such as asphyxiation, anesthesia, injections of the extract of the suprarenal gland (a structure lying just above the kidney) and similar measures, cause increased quantities of sugar in the blood and consequently increased excretion of sugar, and it was shown that insulin, given preliminary to such procedures, will inhibit the appearance of the increased quantity of sugar.

Not until all these factors had been determined, as Macleod himself points out, was the drug administered to man. Had administration of the drug been permitted unguided by the results of the observations on rabbits, it seems almost certain that overdoses might have been given, convulsions would have followed, and there would have been not the slightest indication as to how these convulsions could be prevented or alleviated. But, working with the rabbits, it was possible to show that the convulsions resulting from an overdose are due to a lessened quantity of blood sugar, and that they may be alleviated by the giving of sugar.

Debt to Animal Experimentation.

Thus may another great discovery of scientific medicine be added to the debt of animal experimentation! What a pity that there are still human beings so unreasonable as to wish to remove from scientists the ability thus to use the dog, the rabbit, the frog, and even lower orders of life for this high-minded, wholly humane purpose! It has been shown that the standardization of this product is absolutely dependent on the use of the rabbit; on the day when the use of such animals is not permitted to the scientists, those who may abolish the privilege will have put themselves into the position of bearing the accusation of having removed the chance of life from a million of their fellow citizens. But it is folly to expect for a moment that any rationally minded legislator will ever be led into such a fallacious act! Already the world owes a tremendous debt to scientific experimentation on the lower animals; now insulin has been added to the long account, containing diphtheria antitoxin, arsphenamin in syphilis, vaccines against typhoid in man, serums against meningitis and hog cholera, vaccines against hydrophobia, safety against deadly gases in mines; provision of pasteurized milk, and hundreds of other life protecting and life saving measures.

Let us see what happened when insulin was used on human beings.

The First Clinical Trials.

Heretofore the most serious form of diabetes has been that which occurs in children. One observer reported that of 46 children whom he saw suffering with diabetes, 50 per cent died within three months. Yet among the earliest patients seen by the Toronto investigators was a boy aged 16 years, who had lost 40 pounds during three years of steady decline, and who gained 35 pounds under the administration of this drug within three months.

A few months ago the physicians of the Toronto hospital reported their results in the first 50 cases. The most striking results by far were seen in children, and this, no doubt, is due to the fact that these younger patients retain sufficient of the essential tissues of the pancreas to receive most benefit from the new remedy.

The results of the extract, when properly administered, are striking. In a few days the sugar disappears from the excreted fluid, the chemical substances in the excreted fluid, which indicate a disturbance of the proper assimilation of sugars also are absent, hunger is replaced by appetite, the thirst is lessened, the weight frequently increases, and that pleasant state of the body known as physical vigor is restored.

It reads almost like the glowing accounts of the vendors of snake oil and "ready relief," who used to shout their wares under the flaming torch on the village corner, but in this instance it is the report of conservative, altruistic scientists who have nothing to sell and who have devoted their lives and their discoveries to the service of mankind. It is true.

The Use of Insulin.

Writers on science for the public invariably hesitate when they come to that point in the story covering the administration of the remedy. The reason is not far to seek; one of the oldest stories in medicine concerns a patient who came to his physician with a long tale of what he had read in a household medical book. "Be careful," warned the doctor; "some day you are going to die of a misprint."

As has been pointed out, insulin is a potent remedy. When injected into rabbits in sufficient dosage it produces a fall in blood sugar, and when the concentration has fallen low enough the rabbit indulges in some unusual and uncomfortable symptoms. If the rabbit is given sugar in solution either by mouth or by injection, the sugar concentration rises and the symptoms disappear. If a human being is given too much insulation and his blood sugar fall to a concentration around 0.07 per cent, he promptly becomes aware of similar symptoms. He becomes conscious of some anxiety or of what he will probably call nervousness. He may be tremulous and highly emotional. Very likely he will be pale or he may be flushed and perspire easily and profusely. Should the blood sugar concentration go still lower, there may be acute distress, difficulty of speech and even mental disturbance. But in the human being as well as in the rabbit the symptoms may be relieved by the immediate administration of food. A liberal quantity of orange juice, about four to eight ounces, almost immediately clears up mild symptoms, and a small quantity of glucose given with the orange juice acts even more quickly.

Patients Trained in Use.

Although it is unlikely that any patient with diabetes will undertake or will be permitted to undertake self-administration of this remedy from the first, it is quite likely that intelligent patients may be able to govern their condition satisfactorily after they have been properly instructed.

The observations thus far made have indicated to the physicians throughout the world who are testing the drug, that proper adjustment of the diet and proper relation of the administration of the remedy in the matter of time to the period when food is taken, are very important considerations. The insulin is injected at or shortly before a meal, so as to be operative in the body at the time when the food is being absorbed.

In one instance a patient left the hospital for home after receiving his evening injection of insulin and neglected to secure his dinner. Within a few hours he developed the characteristic symptoms and fortunately was able to secure enough orange juice and sugar to tide him over a most uncomfortable incident. But his case emphasizes the necessity of establishing a proper routine.

Doctor Must Be Expert.

To secure proper results with this remedy it is necessary for the physician to have some knowledge of scientific dietetics and to be able to study reports of the sugar excreted and the sugar in the blood of the patient. He must have a knowledge of the potency of the drug, of the symptoms of danger, of the proper methods of administering the drug, of the method of antidoting unfavorable effects of wrong dosage or wrong diet, and of the correct manner of evaluating the results and the patient's progress.

Fortunately the standards of medical education in the United States today are as high as those in any country in the world. Our physicians are thoroughly trained in physiology, in laboratory diagnosis, in medicine and in diagnosis. Had they instead no knowledge of the basic medical sciences, no training in the laboratory, no information concerning the composition and value of various foods, they would be unable to employ the remedy to best advantage and might in fact discredit its real virtue through misuse. It took scientific knowledge and scientific training to develop this product; it requires the same type of training to use it satisfactorily. Thus this remedy justifies again the plea for a minimum standard of training for all who attempt to treat the sick.

Distribution of Insulin.

Recognizing the value of this substance in the treatment of diabetes, and at the same time its potency for harm if improperly manufactured or wrongly used, the Canadian investigators are controlling its distribution through a committee, established at the University of Toronto. American manufacturers are licensed to manufacture the product; it will also be produced in Canada and in England, and perhaps later in other countries.

The American Medical Association, more than a decade ago, established a body known as the Council of Pharmacy and Chemistry, composed of fifteen representative medical scientists, to consider the composition of and the claims made for any new remedies which might be developed for the treatment of disease. This body has examined hundreds of such products and, until the substances are included in the United States Pharmacopeia, those which are satisfactory for use by the medical profession from every aspect—composition, name, method of distribution, claims, etc.—are described in a book called "New and Non-official Remedies." Both the American and the Canadian preparations have been submitted to the council. In the near future the council will make its report and the use of the drug will be extended from the fifty to one hundred diabetic clinics, in which it has been studied, to all the regularly licensed competent physicians of the country.

The Future of Insulin.

In diabetic coma the discoverers of insulin consider it to be specific. In the diabetes of children, insulin saves life. In patients in whom diabetes is associated with infections such as tuberculosis, or in whom surgical operation is required, insulin is invaluable. And for the vast majority of diabetics whose comfort and whose diet has heretofore been limited, insulin offers perhaps opportunity for a more normal existence. It is not a cure for such diabetics, but it is a remedy which, wisely administered, in relation to a proper adjustment of the quantity and quality of food, will remove from these persons a menace which has heretofore threatened them constantly.

When certain other active glandular principles were first isolated, modern chemistry was called on in the battle against disease and methods were developed for creating the substances in the laboratory without the use of the animal tissue. Already chemists are at work on the problem of producing insulin synthetically. The future may witness even greater progress as the result of these studies.

Tribute to Pathfinders.

Thus culminate the observations made by Aretaeus, the Greek, about 200 A.D., of investigators down through the centuries; of the Germans and Austrians, Mering, Minkowski, Zuelzer, Langerhans, V. Noorden, Weichselbaum and others; of Frenchmen, Hanot, Chauffard, Richardiere and others; of the Englishmen, Willis, Dale, Starling, Smith, Winter and others; of the Japanese, Kamimura; of the Americans, Carlson, Opie, Wright, Allen, Joslin, Woodyatt, Newburgh and a host of others, and at last of the Canadians, F. G. Banting, and Macleod, Best, Collip and their colleagues.

It is a startling testimony to the international character of science; it is an epic of the building of a new temple in which all the nations of the world unite to pile fact on fact in a firm, everlasting structure.

THE MAN WHO FOUND INSULIN.

This is Dr. Fred G. Banting, the young London doctor, who has won a niche in the world's hall of fame through his discovery of a cure for the dread disease, diabetes.

The Romance of Insulin

The discovery of insulin, the new treatment for diabetes described in the accompanying article by Morris Fishbein, M.D., of the American Medical Association, is as romantic a story as many of the world's great mechanical discoveries which have resulted from a lucky chance.

In the third century A. D. a Greek, Aretaeus, wrote a description of diabetes to which little had been added, up to November, 1920. Science had taken account and found that one person in every hundred suffered from this disease, but of cure there was none.

In every civilized country diabetes was being studied, with a view to finding a cure, by physicians, physiologists and chemists. In November, 1920, Dr. F. G. Banting of Western University, London, Ontario, chanced to pick up a magazine devoted to surgery. He was not directly interested in surgery but he turned over the pages. He came to an article that caught his attention, read on—and found a description of the changes that occur in the tissues of a gland, the pancreas, when its ducts are tied off. This article was a match to tinder—it gave Dr. Banting the idea for which physicians had sought in vain for centuries. He investigated, proved his theory, and gave the world of science a new triumph and one of the few authentic instances in which glands have been put to definite curative use.

Six Centuries Ago a Greek Scientist Wrote a Description of Diabetes—Little Was Added Until in November, 1920, Dr. F. G. Banting, Western University, Found the Secret of Insulin.