



## Medical Research and the Discovery of Insulin

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AT THIS moment it is revealed to us that medicine has come to a new birth," wrote Sir Clifford Allbutt in 1919. He then described this new birth as "nothing more or less than the enlargement from an art of observation and empiricism to an applied science founded on research."

To trace the development of the factors that brought about this change would be to outline the highlights of medical history. Though all time the men in medicine who have stood above the ordinary have been those men, who, with minds of high order, starting from the proved facts of science, extended the domain of knowledge into the unknown, through patient, discriminating and skilful pursuit of research.

### *Highlights in Medical History*

The remote beginnings of medical research are to be found a thousand years before Hippocrates. Five hundred years after this great father of medicine, Galen compiled the accumulated knowledge and added to it his own observations. His writings dominated the history of medicine for nearly a thousand years.

Modern research may be said to commence in 1543, when Vesalius published his "Fabrica." Following this, came the works of Gesner, Paré, Harvey, Malpighi, Borelli and Sydenham. By the investigations of these six epoch-making figures in medicine, research received a new impetus. Schwann, Bernard, Müller, Virchow, Haller and Morgagni became the pioneers of physiology and pathology. Morton, Warren and Simpson discovered anesthesia. In 1796, Jenner inaugurated the vaccine for preventing smallpox, thereby eradicating this ravaging disease from all areas where vaccination and revaccination are effectively carried out.

Pasteur disproved the theory of "spontaneous generation" and founded the science of bacteriology. He applied the facts of his investi-

gations and made anthrax and hydrophobia preventable and curable maladies. Lister's work established the principles of asepsis, and paved the way to modern surgery. Reed, Carroll and Lazear sacrificed their lives to make yellow fever areas safe for human habitation. Ross conquered malaria.

Wright, by his discovery of antityphoid vaccine, has, within a few years, reduced typhoid fever to a comparatively rare disease. No better proof of its effect can be given than by a comparison between typhoid fever during the Boer War and the Great War. During the South African campaign, 548,000 soldiers served for two years and seven months; out of every 1,000 soldiers, 123 contracted typhoid fever; altogether 8,248 died of the disease; in other words, more died of typhoid than were killed in action or died of wounds. In the Great War, 420,000 men served for four years and three months; out of every 1,000, only one contracted typhoid fever; altogether there were only fourteen deaths from the disease in the whole Canadian army during the entire war.

### *One Discovery Leads to Another*

The physician and patient of today accept this accumulation of knowledge without question, but we must remember with Sir Michael Foster that:

"What we are is in part only, of our making, the greater part of ourselves has come down to us from the past. What we know and what we think is not a fountain gushing forth from the barren rock of the unknown at the stroke of the rod of our intellect; it is a stream that flows by us and through us, fed by the far-off rivulets of long ago. What we think and say today will mingle with and shape the thoughts of men in the years to come, so, in the opinion and view that we are proud to hold today, we may, by looking back, trace the influence of those who have gone before."



used wells, the old oaken bucket, fire buckets, sewer catch basins, broken glass put on the tops of walls to keep cats and small boys off the premises.

"Mosquitoes can be carried into your hurst from some other and equally delinquent hurst by the winds, if they be strong and fierce—those winds. But the immigrant insects will not stay permanently where they cannot breed. Nor do mosquitoes, as a general thing, travel much beyond 300 yards; certainly not at the utmost beyond half a mile from their breeding places.

#### *Recommends Some Temporary Measures*

"You want to know precisely what steps must be taken? I am glad you ask that, Easybird; it shows you really mean business.

"To go to it then: Petroleum oil (semi-refined, which is less expensive than refined, and more practicable than crude oil) should be used temporarily and not as a valid and permanent means of mosquito destruction. Drainage and filling up the wet places are the surer ways. Oil destroys the wrigglers by choking up their breathing apparatus. One ounce of oil should cover up fifteen square feet of water surface and will remain ten days. Should the wind blow it aside, the oil will generally return when the wind changes. And though eggs may meanwhile have been laid, the returning oil will suffocate the new larvae.

"An ordinary garden sprinkler may be used; or a knapsack sprinkler from which the operator on shore or in a boat may project the oil several yards.

"Goldfish, sticklebacks, minnows, sunfish, the little fish called millions (which find the larvae delicious tidbits), are well enough for garden fountains; but they will not solve the mosquito problem, nor will insectivorous bats, or birds or water fowl.

#### *Takes Community Action to Kill Pests*

"With regard to Stingemhurst as a whole: If you people want to be mosquito free, you must take community action. You have to forget your uppish wealth and be neighborly, and the first thing that you will have to do is to engage a sanitary expert. Pay him what he asks. If you are far seeing you will conclude that in addition to what you have agreed on, he will be entitled to a handsome bonus into the bargain. And everybody will have to get busy—the press, the school teachers, the clergy, the ladies' societies, the board of trade.

"I am going finally to tell you something, Easybird, and I hope you won't feel bitter about it. You Stingemhurstians, for all your wealth



and all your preposterous social assumptions, have not one really big-calibered man among you—except the young doctor, to whose merits and to whose courage you have been oblivious. I will put it this way:

"When I was in Holland, I visited the very modest little cottage in which Peter the Great lived while he was learning ship building. Within is a fine portrait of that real man, with this legend underneath:

*Den Grooten Man is Niets te Klein;* which means, being interpreted, 'To the great man nothing is too slight for consideration.'

#### *It Was Done in Panama*

"Our federal government sent that kind of a man down to the Canal Zone—the late Surgeon-General Gorgas. And let me tell you that it was this Gorgas and no other who made the Panama Canal possible. That was because he and his associates turned the most pestilential spot on the footstool—bar none—into one so healthy that not half a dozen villages, towns or cities in the whole United States could get under its death rate.

There hasn't, this decade or so since, been in that Canal Zone a single case, indigenous to its soil, of malaria, or yellow Jack, or infectious dysentery, or typhoid.

"Are you going to lie down on this record and admit that your dinky little hurst cannot be made as mosquito, or as infection free as Panama? Are you going to let your dear children suffer from a preventable disease—suffer in the way it grips one's heart strings to see. Are you? I pause for a reply."

Here, to Easybird's great relief, we reached his home. All the same there was a gleam in his eye that was indicative of much.

A note had come written in the third person in the best commuter amenity style from Mrs. Delamater O'Shea in answer to that of Mrs. Easybird.

Mrs. Delamater O'Shea begged to make her compliments and acknowl-

edgements to Mrs. Easybird, and would Mrs. Easybird perhaps trouble herself to the extent of going up and taking a look at her own roof gutters.





Research is built on research. Roux was led to his investigation of diphtheria antitoxin by the work of Pasteur. Von Bering, following researches of Roux and Yersin, produced the first diphtheria antitoxin. Roux applied the antitoxin treatment and not only decreased mortality from this disease by 75 per cent., but also by a study of its infectivity, abolished the ravaging epidemics previously so common.

#### *How Insulin Was Discovered*

It is given to few men, as was given to Pasteur, the opportunity to found new sciences and to open up new fields. It was the good fortune of the Toronto group of workers to be permitted to add something of practical importance to the long series of previous investigations in the way in which the body digests and utilizes sugars.

In 1889, von Mering and Minkowski observed that the complete removal of the pancreas produced a severe and fatal diabetes in dogs. Five years previous to this, Villiard and Arnazon had tied the tubes leading from the pancreas and found that the animals did not become diabetic, but that the pancreas shriveled up. Other investigators, using a microscope, found that certain cells of the pancreas—the islands of Langerhans—were not involved, but that it was the other cells which disappeared.

Minkowski was the first to conceive the idea that an extract of the minced pancreas injected into a diabetic dog might relieve the symptoms. Caparelli, Battistini and Vanni prepared extracts and reported favorable effects, but their results were not confirmed. Unfortunately, the injections were accompanied with pronounced toxic effects, which overshadowed any benefit derived.

Following the discovery by Schafer that an extract of the thyroid gland administered to sufferers of thyroid insufficiency relieved symptoms, a large group of observers, including White, Mackenzie, Wills and Sibley, endeavored to supply the deficient hormone in diabetes mellitus, by giving extracts of the pancreas. Their results were not conclusive. Zuelzer, in 1908, by use of an alcoholic extract of the pancreas, obtained favorable results in five cases of diabetes mellitus, but unfortunately toxic results made the continued use of the extract impossible.

Following the discovery by Diamare and Rennie that the islet cells exist separate from the other cells in bony fishes, Rennie and Fraser fed the principal islets of these fish to diabetics, but were unable to show beneficial results. They found this substance too toxic for injection purposes. The search for the elusive hormone was not given up, however. Kleiner, Murlin, Scott and Paulesco continued the physiological investigations on laboratory animals.

In 1912, E. L. Scott prepared alcoholic extracts of the pancreas, and showed that these extracts sometimes relieved certain of the symptoms of diabetes in animals. He endeavored to tie off the pancreatic ducts and to extract the remnant of the pancreas after it had digested the remaining cells, but unfortunately his operation was not followed by complete disappearance of the cells.

This was probably due to the fact that his ligatures were tied so tightly that they caused sloughing of the underlying tissue. Fibrin—the blood clot—was deposited on the surface and the tube was reestablished. Furthermore, Scott was not satisfied with the methods of estimating the percentage of sugar in the blood, and consequently left the problem, which he almost solved, in order to obtain more precise methods.

In 1913, Murlin prepared alkaline extracts of the pancreas and also of the small intestine, and demonstrated that they reduced the elevated blood sugar in diabetic dogs. However, he found that this result could be obtained by the administration of alkalis alone, and the investigation was abandoned. After the war Murlin resumed his investigations and found that the administration of perfusates of the pancreas was followed by an elevation of the respiratory quotient. Thus, he could restore to the diabetic animal some of its lost power of burning carbohydrates.

However, despite the many investigations, in 1920, so vague were facts, that even so great an authority as J. J. R. Macleod stated in his textbook that there is as yet no proof of the existence of the internal secretion of the pancreas, and that there is no proof against the theory that the islet cells are detoxicating centers.

Concerning the solution of the problem, he states: "This consists in seeing whether the symptoms which follow removal of the pancreas are removed and a normal condition reestablished, when means are taken to supply the supposed missing internal secretion to the organism; if they should be, conclusive evidence would be furnished that it is by 'internal secretion,' and not by 'local influence' that the gland functionates."

#### *Canadians Set to Work*

In an article in the medical periodical, *Surgery, Gynecology and Obstetrics* (November, 1920), Moses Barron pointed out the similarity between the degeneration which occurs in the pancreas following experimental tying off of the tubes leading from the pancreas, and the blockage of ducts by gallstones. This led to the deduction that by this means one might be enabled to get rid of the products of the cells in general and to obtain the product of the islets,



free from the destroying influence of digestive ferments.

With this idea, the work on insulin was commenced about the middle of April, with Mr. Charles H. Best, in the department of physiology, University of Toronto.

We first succeeded in showing that the blood sugar of diabetic dogs could be reduced to its normal level by the administration of extracts made from the pancreas of dogs, in which the ducts had been tied from seven to ten weeks. Furthermore, the administration of these extracts rendered the diabetic animals sugar free, and caused a marked improvement in their clinical condition.

Next we showed that extracts made from the pancreas of dogs whose cells had been exhausted by the long continued injection of secretin contained a relatively large amount of the antidiabetic principle, but that these extracts were usually more toxic.

Laguesse had found that there were comparatively more islet cells in the pancreas of the new-born than the adult. Ibrahim was unable to obtain any conclusive evidence of the presence of active protein digesting enzyme in the pancreas of the human fetus till after the fourth month of intrauterine life. The third type of extract was obtained by extracting the pancreas of fetal calves of under four months' development.

The work progressed more rapidly because of the more readily available supply of material furnished from the fetal pancreas. We were soon able to extract the active principle with alcohol from the whole adult beef pancreas. This extract was tried with favorable results on three patients in the wards of the Toronto General Hospital.

#### *Division of Labor in Research*

At the present time medical research is specialized and there is in it, as in all organized walks of life, division of labor. At this stage of our investigation, the Connaught antitoxin laboratory, under the directorship of Profs. Fitzgerald and Defris, provided Mr. Best and Dr. Collip with the facilities for the manufacture of insulin. Prof. Duncan Graham of the department of medicine established means whereby Drs. Fletcher and Campbell could investigate its clinical value, and Prof. J. J. R. Macleod abandoned his work on anoxemia and turned almost his whole laboratory staff on the investigation of insulin.

Under his direction various problems were allotted to pairs of workers and an unparalleled amount of information was gained in a comparatively short time. Not least among these collaborators was Prof. Henderson, in whose department I held my appointment.

I have elaborated at considerable length on the history of the development of insulin,

because it exemplifies the fact that research is built on research. At the present time, we have insulin, but we do not know the exact manner of its action. We know that the deficiency of insulin is the cause of diabetes, because when this deficiency is supplied, the symptoms are relieved, but we do not know the cause of the deficiency. We know that the insulin mechanism is related to other glands of internal secretion, particularly the suprarenals, but we are far from a complete knowledge of their interaction, without which a complete understanding of the disease cannot be attained.

Diabetes is not solved. The pathological findings do not bear an exact relationship to the clinical severity of the case.

Recently Dr. Joslin of Boston sent the pancreas of a patient who died in diabetic coma to Mr. Best, who was able to extract from it abundant insulin. Mann has found that the removal of liver in dogs is followed by a rapid and extensive fall in the percentage of sugar in the blood. Bornstein and Holn, working in Germany, and we, in our own laboratory, have found similar fall is obtained after the removal of the suprarenals. Pituitrin augments the action of insulin. Mr. Best has been able to extract insulin from the tissues of every organ of the animal body. Woodyatt and others have injected very large quantities of glucose into animals and cannot adequately explain its disappearance.

These and other unexplained problems challenge the research worker in carbohydrate digestion at the present moment. Their explanation is necessary before diabetes can be explained and its cause known. I shall not be satisfied until the cause of diabetes is understood and until preventive treatment is instituted or until the early and mild cases at least can be adequately controlled.

#### *Discoveries Come When World Is Ready*

This history of medicine has shown that discoveries usually come when the time is ripe for their reception. Had insulin been given to the world fifteen years ago, we would not likely have had the valuable contributions of Allen, Joslin, Woodyatt, Wilder and others in the important field of dietetics. Nor would there have been accurate methods for estimation of blood sugar, acetone or respiratory quotients.

The discovery of insulin, in turn, opens up new and wider fields and in like manner every research in the field of medicine assists the advancement of other branches. Here we find further reason for urging research. When the scientific world is ready the cause and cure of cancer will be forthcoming.

The results of the combined efforts on the part of medical research workers has led not only to the alleviation of human suffering, but also to the prolongation of human life. Quoting



Dr. John R. Williams of Rochester, "In the seventeenth century in London, from what is known, the average age at death was twenty-one years. Seventy-five years ago it was thirty-five years. Today, it is nearly sixty years."

From statistics available, it is estimated that an average of ten years has been added to the expectancy of life during the past twenty-five years. A medical actuary expert in discussing this subject said "our annuity system has gone blooey." Referring to this insurance company he said that during the past year they had paid out \$400,000 in annuities in excess of their estimates.

The greatest contributory factor in producing this result has been the activities of preventive medicine. Ravaging epidemics of diphtheria, smallpox, typhoid and all the communicable diseases have been investigated, understood and controlled. Even tuberculosis is being curtailed.

### *Inward Joy of Discovery*

How have these blessings come to us?

They have come from the minds of individuals who have the true research spirit. From a study of the lives of such men as Pasteur, Lister and Bernard, one is convinced that it was the highest of ideals that compelled them to work. There was no desire for fame, publicity or self-aggrandizement, but for the inward joy of discovery.

Well may Mark Twain ask the question, "What is it that confers the noblest delight, what is that which swells a man's breast with pride above that which any other experience can bring him? Discovery." This inward joy is the greatest source of inspiration for further work. Inspiration that comes from without is of a positive and negative character; the former in the way of kindly, helpful encouragement of friends, the latter in the way of doubtful, pessimistic, destructive criticism of individuals, who try to dampen enthusiasm.

Research work calls for a special type of mind. It is possible to draw a rough distinction between the teacher and the original investigator. While the former must be well informed and capable of imparting his knowledge, the research man must add to his knowledge a facility for constructive association of ideas.

### *Place of Research in University Life*

Henry S. Pritchett, president of the Carnegie Foundation for the advancement of teaching, says: "The part that research ought to play in medical education is so necessary and so vital, that its importance cannot be overestimated. On the other hand, so-called research offers the rarest opportunity for exploitation which our institutions contain (although this process has not reached the same stage in the professional school that it has reached in the college and the university). Every college and university covets

the reputation of being a center of research. It is more anxious that its teachers should have the name of conducting scientific investigations than that they should be able to teach fruitfully and successfully. The result of this striving is that the thing that ought to be the greatest inspiration toward good teaching has become too often an excuse to escape the primary duty of teaching."

We do not know whence ideas come, but the importance of the idea in medical research cannot be overestimated. From the nature of things ideas do not come from prosperity, affluence and contentment, but rather from the blackness of despair, not in the bright lights of day nor the footlights' glare, but rather in the quiet undisturbed hours of midnight, or early morning when one can be alone to think. These are the grandest hours of all, when the imagination is allowed to run riot on the problem that blocks the progress of research, when the hewn stones of scientific fact are turned over and over, and fitted in so that the mosaic figure of truth, designed by Mother Nature long ago, be formed from the chaos.

In the medical literature of today, we have textbooks, scientific treatises, journals and magazines. One wonders if there is an end of knowledge. I fancy the pages that are covered with cancer literature, if spread out, would cover the state of Illinois. Yet, its solution is not at hand. I sometimes wonder if we are helped by too full a knowledge of medical literature. I must frankly confess that, had I read all that was written on diabetes and known all of the conflicting views and theories, I would probably never have tackled the problem.

### *Must Put "Affections in Cold Storage"*

The young man who devotes himself to medical research must familiarize himself with the first paragraph of Osler's "Alabama Student." It begins as follows:

Chief among the hard sayings of the Gospel is the declaration, "He that loveth father or mother or son or daughter more than Me is not worthy of Me." Yet the spirit that made possible its acceptance and which is responsible for Christianity as it is—or rather, perhaps, as it was—is the same which in all ages has compelled men to follow ideals, even at the sacrifice of the near and dear ones at home.

The man who wishes to make a success in research work must be prepared to work. He must sever his connections with labor unions that restrict the hours of his labor. He must be prepared to live, move, and have his being in the laboratory, eating and sleeping beside his work, if need be. Matrimony and research have seldom gone together. Very many brilliant young men have been overwhelmed by domestic responsibilities and have been lost to research. Here again it is well to quote Osler: "Put your affections in cold storage."



The vital statistics of the city of Toronto illustrate the fact that whereas infant diseases, infectious diseases, including tuberculosis, show a marked decline in death rate, there is, on the contrary, a marked increase in deaths from heart, artery and kidney disease, cancer and diseases of metabolism. A glance at these vital statistics shows a tremendous increase in mortality from cardiovascular-renal disease. In the city of Toronto in 1913, there were 858 deaths as compared with 1,353 deaths in 1923, or an increase of about 60 per cent. During the same time the population increased from 445,000 to 529,000, or an increase of approximately 20 per cent. In the same period of time, deaths from cancer increased from 336 to 605, and tuberculosis decreased from 467 to 351.

It is evident, therefore, that cancer, terrible as it is, accounts for less than half the number of deaths that are attributable to heart, arteries and the kidneys. There, is, thus, abundant

opportunity for the young man with ideals, ideas, enthusiasm and willingness to work.

Medical research is the most truly international commodity we possess. It knows no protective tariff, no embargo, no boundary line to prevent its free dissemination for the good of all. At present it is the common language and common spirit among the nations.

May I make bold to hope that American and Canadian science, depending as it does on the efforts of individual minds, may harmoniously progress hand in hand, until that day is reached when they shall have contributed the maximum of good to the greatest number, and have brought the people at large to realize that science is the search for truth, that a true knowledge of God's creation dispels superstition, fear and disease, brings happiness, peace and prosperity, and leads to that humility with which the informed intelligence recognizes the omnipotence of the Creator?

## *What Do We Talk About?*

AND when I wouldn't give him a date for the next night, he got sore——."

"There wasn't a bank in town that would lend us a nickel in those days. Now——."

With women it is men, and with men it is business! At least that is what three psychologists have found, after analyzing chance conversations of persons on Broadway and in Columbus, Ohio.

### *Well Persons Rarely Discuss Health*

As for health, it has little conversational interest to anyone who is well.

Listening in on the conversation of others has always been an absorbing pastime, and many a dull journey has been enlivened for a lonely traveler by overheard conversation.

Two psychologists, M. H. Landis and H. E. Burt of Ohio State University, recently analyzed 500 conversations which they overheard in that community, with a view to finding out what are mankind's chief interests. They compared their findings with those of the psychologist, Henry T. Moore, who several years ago made a similar analysis in New York of conversations heard on Broadway.

The two Ohio scientists included in their investigations the conversations of persons in restaurants, at basketball games, in theater lobbies, in front of store windows, on the university campus, in barber shops, in churches and on the street.

### *Business and Amusements, Men's Topics*

Conversations were classified under ten headings: business and money, men, women, clothes and decoration, sports and other amusements,

college work, health, self and weather. The results at Columbus, Ohio, in general agreed with those observed on Broadway. The psychologists tell of their finds in the *Journal of Comparative Psychology*.

Men's most frequent topic is business—49 per cent. in Columbus and 48 per cent. in New York. If sports and other amusements are combined, these topics have a frequency of 15 per cent. at Columbus and 14 per cent. in New York. The third topic of men's conversation is men—12 per cent. in Columbus and 13 per cent. in New York.

### *Men and Clothes Are Women's Favorites*

Women's leading topics are men, 22 per cent., and clothes, 19 per cent. For New York, the figures were men, 44 per cent., and clothes, 23 per cent. The next topic is other women, about 15 per cent.

In mixed company, men most frequently talk to women about amusement, and next of business and money. They further seem to talk to women considerably about themselves—17 per cent.—which is more than when talking to other men.

Women most frequently converse with men about amusement; secondly, about clothes; thirdly, about themselves and about men.

The results were classified also as to the social status of those concerned. Business people talked about business and money in 70 per cent. of cases, as compared with 43 per cent. for industrial workers and 9 per cent. for students.

Although health was one of the subjects catalogued, it is important to notice that it had little interest for those who were well.