wires in cables, an actual physical circuit had to be provided for every connection that was made. The advent and development of loading coils and amplifying devices, both products of the laboratory, did not alter this necessity, although they did increase the distance over which communications could be given economically.

Until fundamental science, much of it involving new knowledge, was, through the coordinated work of industrial research, directed to the problem of extremely low-cost channel provision, there was essentially only one known way of providing a multitude of non-interfering channels along a common route. This was to assume that the electrical impulses over each channel were essentially alike and by means of geometrical and mechanical arrangement to reduce to a minimum the deleterious effects of transfer of energy from any circuit to its neighbors.

Recently, however, thanks to the research laboratory, operating in a myriad of fields and with organized utilization of the results in these fields, an entirely different method of providing large numbers of channels has been achieved and the way opened to an unknown indefinite extension. There is no time here to elaborate the niceties of the method. It is sufficient to say that it is what has commonly come to be designated as the carrier method, by which a single physical circuit can be made to transmit simultaneously a large number of non-interfering conversations by means of apparatus which is relatively simple and reliable and whose cost when apportioned among the several channels provides these channels much more economically than was possible under the older art. While there are definite limitations in the field of use of this method, it bids fair to have wide application over the longer distances. In its most advanced application, namely, that of the so-called coaxial cable, which is now undergoing trial in an experimental installation between New York and Philadelphia, many hundred telephone conversations can be carried on over a single pair of physical channels.

Achievement of this and similar less spectacular results imposes a burden of extreme nicety and reliability on the functioning of many devices, since failure of any one will disrupt not a single conversation but a multitude of conversations. That such multiple transmission can even be contemplated seriously is high tribute to the power of scientific research which makes it possible.

Broadly speaking, the main emphasis of all research in the telephone field is directed toward the goal of producing terminal apparatus, switching mechanisms and channels of communication of great reliability and minimum cost, both first cost and cost of operation and maintenance—all to the end that facilities can be provided in the profusion needed for a uniform no-delay service at an expense to the subscriber which will have minimum tendency to restrict usage where telephony is the indicated preferred method of communication.

In two of the main sectors, namely, those of switching and trunk channels as between central offices or between cities, the purely technical problems of unit cost reduction are frequently made somewhat easier by the fact that certain of the elements lend themselves to wholesale treatment. In much of the third sector, however, namely, that of local distribution to the subscriber, the case is essentially one of dealing with a retail problem. Here, even if the equipment itself and the channel connecting it to the central office could be furnished at extremely low cost, there would still be a substantial item of investment involved in the fact that installation and maintenance cost would be relatively high. Even here, however, it is to the research laboratory that we must look for most of such help as it is to be anticipated.

EARLY WORK ON INSULIN[1]

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I first wish to thank the Mellon Institute for their kind invitation to be present on this occasion. I wish also to congratulate you on this fine new research laboratory. It is a monument to the Mellon family and also a monument to the successful work of the institute in the past.

Although I have heard much of the Mellon Institute it was not until I read the book of your director that I understood the true significance and scope of your

endeavors. May I express the hope that your future activities will be crowned with equal or even greater achievement.

It was with great pleasure that I observed that the Mellon Institute is including in its activities certain problems in medical research. It is to be hoped that you will undertake research on other major problems in medicine and that you may even organize an attack on cancer.

The field of medical research is so wide that it is necessary to specialize. I did not therefore feel that I could adequately cover the field of internal secretions,

as requested in your invitation, but asked that I be allowed to speak on the internal secretion of the pancreas.

This task is more difficult than might be thought, because it is now fourteen years since I have done experiments on the internal secretion of the pancreas. I have, however, retained an active interest in the subject of diabetes. A very great deal of research had been done on the pancreas previous to 1920. It was known that there were two types of cells. One group, called acinous cells, produce powerful enzymes which are poured into the intestine for the digestion of food. These cells produce the external secretion. The other cells are fewer in number and occur in groups and are called the "Islands of Langerhans." These are the cells which produce the internal secretion.

It was known that the extirpation of the pancreas resulted in diabetes. It was also known that if the pancreatic duct was tied there was an atrophy of all the glandular cells which produce the external secretion, but the animal did not become diabetic. Many investigators had tried to make active extracts of the pancreas that would be of value in the treatment of diabetes.

The original hypothesis on which the work on insulin was based was that the enzymes of the cells of external secretion destroyed the active anti-diabetic product of the cells of internal secretion. Our whole effort was directed, therefore, to eliminating the destroying substances. We first ligated the pancreatic ducts in a number of dogs, waited some weeks for the acinous cells to degenerate, then removed and extracted the remaining cells. This extract was tested on a dog that had been rendered diabetic by removal of its pancreas. It was found that extracts made in this way contained an anti-diabetic substance, since they improved the clinical condition of the animal and decreased the amount of sugar in the blood and urine. Active extracts of the pancreas were also made by exhausting the glands of external secretion and thus getting rid of their destroying enzymes.

It was then found that an extract made from the pancreas of foetal calves of under 4 months' development contained a powerful anti-diabetic substance. Finally we found a chemical means of extracting the active anti-diabetic substance from the whole adult pancreas of the abattoir animals.

The production of a purified product then became the problem of the chemist. To Best, Collip, Shaffer, of St. Louis, and Clowes, of the Eli Lilly Company, must be given the credit for the early work on the purification. I would like to again pay tribute to the admirable cooperation of Dr. G. H. A. Clowes and his research group of the Eli Lilly Company in the early

struggle in extraction, purification and large-scale production of insulin.

From experiments on animals it was found that the physiological derangements caused by the removal of the pancreas could be corrected by the administration of insulin. It was proved that the increase of sugar in the blood could be lowered to normal or even subnormal levels; that sugar could be stored in the liver as in a normal animal; that whereas a diabetic dog can not burn sugar, it could be made to do so when insulin was administered; all the signs and symptoms of diabetes could be relieved; and the life of the depancreatized dog could be prolonged. Thus it was believed that insulin was the internal secretion of the pancreas and that its administration would relieve the symptoms of diabetes.

From this knowledge of the experimental work on animals we were able to predict the result of administering insulin to humans. One of the main factors in this prediction was that of diet. It must be remembered that when insulin was first used clinically diabetes was being treated by diet. Both patients and doctors had fixed ideas concerning what they should eat. Some were taught that diabetics should starve until they became sugar-free and then eat weighed amounts of fruits and vegetables which contained small amounts of sugar; some followed the high fat diet, while others used a combination of these two.

The pancreas of all diabetics, regardless of the severity of the disease, produces some insulin. Taking into consideration the variations in diet, the object of the treatment was to supply insulin in just sufficient amounts to compensate for the deficiency in the patient's pancreas.

From the physiological point of view there seemed no reason why a diabetic should not eat a normal diet. As early as August, 1922, one of our most severe diabetics was given a diet which included bread and potatoes and was kept sugar free by the use of insulin. When a group of diabetic specialists visited Toronto in November of that same year they would scarcely believe the records of this patient.

The time of administering insulin is an important factor. In order to have its action concurrent with the absorption of food it is advisable to give the injection 20–35 minutes before a meal.

If too much insulin was given we observed in the humans, as had been previously found with animals, that the blood sugar fell to subnormal level. This fall in blood sugar was accompanied by symptoms which we now call insulin shock. The administration of glucose caused a rapid return of the blood sugar level to normal and relieved the symptoms.

One of the most dreaded complications of diabetes

was coma. This condition was explained by saying that "fats only burn in the fire of carbohydrates." When the production of acetone bodies—aceto-acetic, beta hydroxy-butyric and acetone—become greater than the excretion these ketone bodies accumulate, producing drowsiness and coma. Previous to insulin coma was a common occurrence. Now I believe it is less common. Insulin was specific for coma, since it caused sugar to burn and with it the fats were completely oxidized.

Another complication of diabetes that was met with in the older patients was gangrene. In the pre-insulin days operation was dangerous and the patients usually died following the operation. Now diabetics can be safely operated upon because insulin controls the blood sugar and acetone production.

The early clinical results were obtained from an insulin which we now know contained impurities. Biochemists took up the problem of purifying the product. Abel, of Baltimore, in 1926, was the first to prepare insulin in crystalline form. The medium from which he obtained his crystals contained ammonium acetate, brucine and pyridine. The isolation of the crystals was attributed to the fact that the acidity could be adjusted to the isoelectric point of insulin, so slowly and so accurately that a supersaturated solution was obtained. Scott, of Toronto, working with Harington, of London, obtained crystals from amorphous insulin using a buffer solution of ammonium acetate and saponin. The yield of crystals produced by these methods was irregular.

On searching the literature Scott found that the pancreas contained considerable quantities of zinc (according to Lutz) and of cobalt and nickel (according to Bertrand). He then found that when traces of zinc were added to a buffered solution of amorphous insulin crystals were readily obtained. He explained the results of the saponin crystallization by the fact that the saponin contained zinc as an impurity. On examination it was found that Abel's crystals also contained zinc. Scott proceeded to test large numbers of metals and found that cadmium, nickel and cobalt could also be used in the crystallization, but were less satisfactory than zinc.

In the meantime, refinements were introduced into the methods of production of the insulin that was being used clinically. With the elimination of impurities the insulin was more rapidly absorbed and the duration of its effect was lessened. This made it necessary to increase the number of doses in order to maintain a patient free from sugar. Since insulin could only be taken by hypodermic injection the result was an added inconvenience to the patient.

Hagedorn, of Denmark, sought to prolong the effect of insulin by adding protamine, which was obtained from sperms of rainbow trout and mackerel. Hagedorn and his colleagues, 1933–35, found that the addition of protamine to their insulin so delayed the action that the day's supply of insulin could be given in one injection. This was the greatest advance in the treatment of diabetes since the discovery of insulin. Scott found that when protamine was added to zinc-free amorphous insulin, there was little or no delay in the rate of absorption. If, however, zinc was added a combination occurred between the insulin and protamine with the characteristic slowing effect of the protamine. It would seem that the Danish insulin contained sufficient zinc or other specific metal to produce this combination.

Ordinary insulin, as used in Canada and the United States, is made by dissolving amorphous product which contains from 16 to 20 units per milligram. Protamine zinc insulin is made by adding definite amounts of zinc and protamine to ordinary insulin. By the addition of zinc to a solution of amorphous insulin 89 to 90 per cent. can be crystallized. Crystalline insulin has a potency of 23 units per milligram.

Another modification is being tested, namely, zinc alone to insulin. Scott had found in dogs that there was a prolonged blood sugar lowering effect following the injection of zinc insulin. This insulin is now being tested clinically by Dr. Hipwell, who has found that the effect of zinc insulin is intermediate between regular insulin and protamine insulin. It is too early to speak of the clinical value of this form of insulin.

The original hypothesis was that insulin could not be extracted from the pancreas because it was destroyed by the pancreatic juice. It is interesting to note that even the most purified insulin is digested by both trypsin and pepsin. Insulin is a protein from which nine amino acids have been isolated. In the digestion of insulin the total activity is lost when only 25 per cent. of the protein has been split.

Dudley, Rosenheim and Rosenheim found that the insulin prepared by the picric acid method contained spermine. This spermine was found to be a normal constituent of pancreas. Lutz found that the pancreas contained zinc. It may have been the presence of these substances in pancreas which resulted in the slow action of the early insulin preparation.

The chemistry of insulin has been extensively investigated; the clinical application has been widely accepted. It is estimated that over one million people receive insulin each day. Although much of the physiology is known, we do not yet know how insulin enables the body to utilize carbohydrates nor do we know the cause of diabetes.