

## INSULIN, OLD AND NEW, IN THE TREATMENT OF DIABETES\*

BY ELLIOTT P. JOSLIN, M.D.,

*Boston*

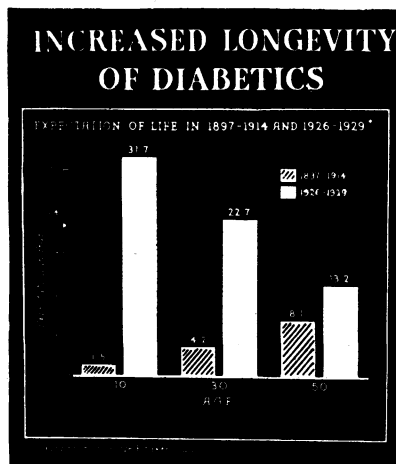
WITH great modesty I appear before the Ontario Medical Association in whose membership are those who gave insulin to the world. Nothing I might say relating to that great discovery could express adequately my gratitude to those Canadian investigators who produced it, or measure the joy I have experienced since insulin was placed in my hands on August 7, 1922. Facts speak louder than words, and here is my testimony to the value of insulin, based upon the lives of my patients and the computations generously conducted for me by the Metropolitan Life Insurance Company.

The expectation of life of my patients at ten, thirty and fifty years of age, regardless of the duration of their disease, as determined by their death rates subsequent to the first observation, has been computed for two periods, 1897 to 1914 and for 1926 to 1929. For children at 10 years in the earlier period the average expectancy was 1.5 years, but now it is 31.7 years. Whereas they

did not live to reach their twelfth birthday, they now can be expected to attain their forty-first, even without any allowance for possible, nay probable, advances in treatment. Present these facts to the parents of a diabetic child, and can there be any hesitation on their part to use insulin? If there is, present the same to the Judge and Jury and let them decide what action should be taken.

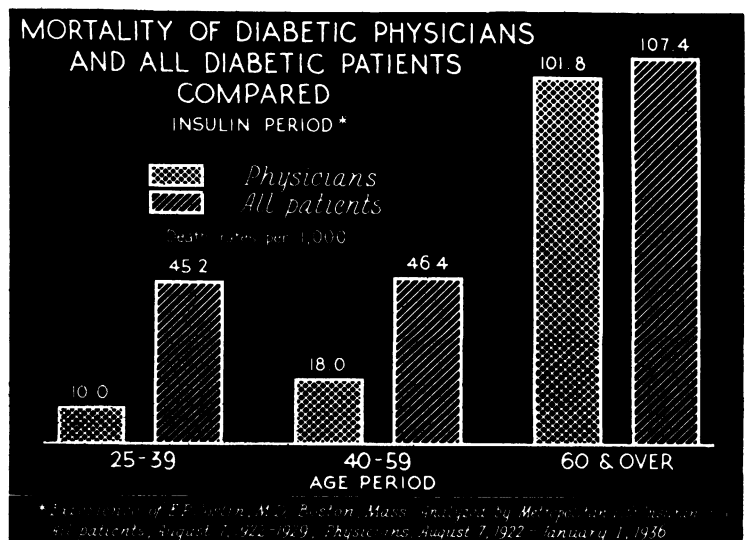
The expectancies for the two similar periods at 30 years of age vary nearly as much; they are 4.2 years and 22.7 years, and for the age of 50 years also they show strong contrasts, 8.1 years and 13.2 years, respectively. But I have another line of evidence to offer you about the efficacy of insulin, namely, that obtained from my diabetic doctors. Doctors know more about diabetes than the laity, and doctors want to continue their practices. From what they have learned about diabetes by study and observation they are in a position to decide whether the treatment of diabetes pays. Therefore, it occurred to me that the records of my diabetic doctors ought to show the results of a knowledge of the disease. In

\* An Address delivered at the Fifty-sixth Annual Meeting of the Ontario Medical Association, London, Ont., on May 28, 1936.



Based on death rates at each age, subsequent to first observation, regardless of duration of diabetes

Chart 1



\* Prepared by E. P. Joslin, M.D., Boston, Mass., analyzed by Metropolitan Life Insurance Co., patients, August 7, 1922-1929, Physicians, August 7, 1922-January 1, 1936

Chart 2

Chart 1.—The expectation of life of the diabetic child and young adult has increased many fold, and even for the fifty year old diabetic, has risen over 50 per cent. The increased longevity of diabetics is due largely to insulin which has reduced diabetic coma, and minimized the risk of infections and surgical complications. Modern treatment adds years to the productive life of diabetics. (Prepared by the Metropolitan Life Insurance Company.)

other words, is it worth while to teach a diabetic a good deal about his ailment?

Three hundred diabetic doctors have consulted me since 1898, and of this number 92 have died. Again, through the courtesy and cooperation of the Metropolitan Life Insurance Company, a statistical analysis has been made of this group. (The case numbers and not the names of the doctors have been submitted for study.) This demonstrated, first of all, that since 1922, the date of the introduction of insulin, diabetic coma has practically disappeared as a cause of death among doctors. It has amounted to but 3 per cent. This is all the more notable because diabetic coma when it develops in adult life is a serious complication, and recoveries are far less frequent than in childhood. Under efficient treatment nearly all cases of coma in children can recover. We have lost one case in 87 children 15 years of age or under, and, indeed, this is the only one among the 134 whose diabetic onset was under 15 years, or 0.7 per cent since 1933, but in adults the fatal outcome has risen to between 25 and 40 per cent for some of the decades. Doctors realize the danger of coma. Doctors know how to avoid diabetic coma, and consequently do not expose themselves to it. Doctors are unwilling to die of diabetic coma. If doctors will not die of diabetic coma, why should their patients?

Another comparison can be made between my diabetic doctors and my other diabetic patients of similar age groups. Whereas between 25 and 39 years of age the death rate per 1,000 for diabetic doctors is 10, among all my diabetic patients it is 45; at 40 to 59 years the rates are 18 and 46.4, and at 60 and over, 101.8 and 107.4 respectively. Finally, I will add that the average age at death of all my patients is 63 years but of my doctors is 68 years, and I am trying hard to raise the average to the Psalmist's three score years and ten. Diabetic doctors know how to profit by treatment and so keep alive. For years I have realized that many diabetics, because of their wisdom, were able to live longer with their disease following its onset than their non-diabetic friends of equal age. Indeed, approximately 400 of my patients have been given medals for this achievement. Today the percentage of my patients living over 20 years is ten times what it was prior to 1914.

All that I have said thus far supports my life's endeavour, namely, to prove that knowledge of

his disease protects the diabetic. It further serves to drive home the idea that the discovery of insulin has revolutionized the treatment of diabetes.

*The education of the diabetic.*—The education of diabetics can be accomplished by books, moving pictures, class teaching, and individual instruction, but perhaps most of all they can profit from contact with other patients. The personal element and the spoken word are the most important, because what one type of diabetic needs would be superfluous for another. The disease is an interesting one anyway, and it is easy to impart information and this falls on willing ears.

At the George F. Baker Clinic we furnish the patients with printed material relating to diet and hygiene, encourage them to secure a manual on diabetes for a guide at home, and approve their following the outcome of their daily tests. There is a daily class room exercise at 10.30 a.m. with a doctor as a teacher. It lasts forty-five minutes, and we endeavour to make it systematic and to cover the subject of diabetes in one week. Fundamentals are emphasized. The class often becomes a clinic and sometimes an experience meeting. In addition, the Teaching Diabetic Nurse gives on Sunday a classroom exercise for the benefit of those who are only in the hospital for a week-end or brief stay.

Classroom instruction is supplemented by individual instruction, either in the office or by the Teaching Diabetic Nurse at the bedside. Appointments are made, and there is an endeavour to talk with the patient in the presence of his family. Indeed, my colleague, Dr. Root, has found it most helpful one night a week to meet the relatives of our surgical patients who have lesions of the lower extremities and to instruct them in the care of those who are soon to be discharged.

The Wandering Diabetic Nurse is another agency for instruction. Originally, she spent nearly all of her time in the homes of the children, but this last year she has visited and helped at the other end of life in the supervision of the very old children in their own homes. In the summer she has charge of the Clara Barton Homestead Camp for Diabetic Girls at North Oxford, Massachusetts, at which we have a group of 100 children in the course of two months. This summer in all we hope to have 175 children in various camps.

*Diabetics today are living a long, long time.*—Do you physicians realize that the chances are that the diabetic child of 10 years of age who enters your office will still be living when you give up practice? Doctors work only about 30 years, and the diabetic child will live as long. In fact, I am convinced that the average diabetic who develops diabetes in 1936 will certainly live 20 years! This being so, how are you and I to hold our diabetic patients, not for their but for our lives? And the answer is—only by the application of knowledge to the disease. At each visit one must be able to tell his patients something more than they have read in the newspapers and weekly publications, something which they will recognize as directly helpful. That is why I have travelled more than 5,000 miles these last few weeks; it is one of the reasons I came here today—to learn something so that I can go home and treat my patients better. And now may I pass on to you a few practical observations and suggestions about the treatment of diabetes, gathered here and there and from experience.

*Laboratories and laboratory tests.*—A doctor and his wife brought me this month their little girl, not quite four years of age. She had shown a little glycosuria, and according to their story they took her to a hospital—they said a children's hospital—for diagnosis. She was given a sugar tolerance test. The house officer missed the veins so many times that when he came to perform the last tests the tears ran down his cheeks. Incidentally, when the blood of the doctor's wife was taken she told me she fainted. Moral.—Always assure yourself that capillary blood sugars shall be taken from a child, and, if you follow my rule, you will never allow the blood of a patient to be taken from a vein except when lying down. Incidentally, remember that capillary blood is the equivalent of arterial blood, that in the fasting state capillary and venous bloods are identical, but after food the capillary may be 30 milligrams more than the venous.

Laboratories are splendid; without them diabetics cannot get adequate treatment. They should be within the reach of every family doctor, just as they are available for every hospital doctor. From them for poor patients he should be able to secure tests for sugar in blood or urine free, at cost for indigent patients, and at reasonable rates for paying patients. This

becomes possible when we remember that wholesale tests are cheap, single tests expensive. Increase the output of the hospital laboratory; reduce the expense of individual tests. (Later in the day I visited your government laboratory and found you have the service I would like to see inaugurated in Massachusetts.)

Laboratories, like obstetricians, must function day and night. Diabetics and babies are alike; they need instant care. Babies sometimes will be born between Saturday noon and 9.00 a.m. Monday, and likewise coma cases may develop at such inconvenient hours. Further, laboratories must function promptly. Tests for CO<sub>2</sub> combining power of the blood plasma in diabetic coma do not aid in the care of the patient if reported twelve hours after death.

Doctors need for their diabetic patients "diabetic islands of safety". Such I believe to be the hospitals with well equipped laboratories, capable of work day and night and holidays. Such hospitals also should have a Teaching Diabetic Nurse to instruct the other nurses in diabetic nursing and also the diabetic patients as well. If called upon to help doctors in the vicinity in the instruction of their patients she should be available. Our Wandering Diabetic Nurse is of great service in this way.

*Heredity and obesity.*—At Sioux Falls, S.D., a few weeks ago Dr. Gage collected 23 diabetic patients, and I had the pleasure of having them on the platform for a clinic before the South Dakota Medical Society. On the front row I placed four brothers and sisters, all diabetics; the fifth child in the family already had died of the disease. Never forget that diabetes is hereditary. Seek for the source of your case and train the patient to be on the watch for the other diabetic members in his or her family. The early diagnosed diabetic, like the early detected case of tuberculosis, is the one who does the best. And since obesity is the most common cause of diabetes in the hereditarily predisposed, teach your patient to protect his relatives by urging them not to get fat. The diagnosis of diabetes places upon the diabetic individual the protection of his family.

*Protamine insulin.*—In the *New England Journal of Medicine* for today, May 28, 1936, will be published the second report upon protamine insulin from the George F. Baker Clinic. I cannot help making a few excerpts from it (with the consent of its Editor), but in addition

there are certain new features regarding its use which I wish to call to your attention. Three cases merit repetition.

#### CASE 1

"Eleven year old Blair W. showed 10 per cent of urinary sugar upon the morning following the discovery of his diabetes, and began the use of protamine insulin forthwith. Thirty units were given before breakfast on the first day, 50 units on the second, third and fourth, and upon the fifth day the urine was sugar-free although the patient had received in the previous 24 hours 210 grams of carbohydrate and 1,900 calories. He had no reactions and eleven days later, while at home, was sugar-free with a normal blood sugar. By that time his insulin had been reduced to 24 units before breakfast. It is true he was a fresh case and a child, but contrast this experience with the inauguration of treatment with former methods." (October, 1936, alive, sugar-free, protamine insulin 16 units.)

#### CASE 2

"Mrs. S., a nurse 36 years old, so crippled with rheumatoid arthritis that exercise was impossible in the treatment of her diabetes of one year's duration, weighed 84 pounds in July, 1935. To control her diabetes she required insulin in enormous amounts, given in 4 to 6 doses daily for six months. At one time she took as high as 530 units a day. Since January she has shown improvement, her weight has risen to 117½ pounds and the insulin was decreased to 240 units administered before meals and on retiring. Upon January 23rd she began protamine insulin, and now in April her diabetes is equally well controlled with insulin once daily, 120 units of the old and 120 units of the new."

#### CASE 3

"Ruthie's parents told me that since her severe reaction ten years ago they had not dared to let her sleep alone. This last autumn, the week after entrance to a college in Boston, while at lunch with her mother at a restaurant, she had so violent a reaction it was necessary to call an ambulance and remove her to a hospital. Immediately she began protamine insulin and is now taking 40-0-[36]. Her mother says, 'Since Ruthie commenced protamine insulin she has had no reactions. She sleeps alone. You cannot tell, Dr. Joslin, what protamine insulin means to her father and me.'"

More than 100 of my patients have been given protamine insulin and the greater part of them continue to use it. No patient taking it has developed coma, acidosis, or any complication common to diabetics, such as lesions of the feet or skin. The number of doses has been reduced from six to one or two daily. In only one instance has there been local irritation from the protamine insulin, and that patient has not been under my continuous observation. Reactions have occurred and at times with little or no warning. They occasionally have reached the convulsive stage, but nearly always this has happened when old insulin and new insulin have been employed in the same twenty-four hours. The reactions may last for a considerable period and require repeated administration of carbohydrate for their relief. One of the patients

developed a cerebral complication, but I am not convinced that it had anything to do either with the reactions he had had in years gone by with old insulin or his recent reactions with new insulin. Protamine insulin I consider a real advance in the treatment of diabetes, but I do not believe that we know the best methods of employing it, nor do I think that it should be distributed yet for general use. The old insulin we understand and we all know that it always works. We must not undermine confidence in insulin by giving to practitioners a preparation, although it may be better in some respects, whose action is not thoroughly understood. The technique of the manufacture of the protamine insulin is improving and I can say definitely that our results with the newer preparations are more uniform. I suspect that it will not be long before it is still more reliable.

Our administration of the protamine insulin can be improved. It is not a matter of indifference to inject 20 units of old insulin twice a day and then change over to the injection of 40 or 50 units of protamine insulin in a single dose. More pains must be taken with the actual technique of injection, and one must also select more carefully the sites for the injection. An injection into the firm tissues of the arm may work quite differently from an injection the next day into the looser tissues of the thigh, and I imagine the variation might be still greater if the drug were introduced into the very loose subcutaneous tissue of the abdomen.

The strength of the preparation may be important. The single doses of the protamine insulin are larger, and, therefore, U-40 insulin is too bulky, but just how U-80 protamine insulin will act I do not know. Perhaps we should never inject more than 1 c.c. of insulin in any one locality.

Shall we inject the protamine insulin subcutaneously or intramuscularly? This is another question open for investigation. The muscles act with the help of insulin. Evidently we must study the new insulin under conditions of rest and activity. If the patient is exercising violently, will he be capable of drawing upon his deposit of protamine insulin just as it is required, or will it be released too slowly or too rapidly? Here are fascinating problems, but not all of them are appropriate for the general practitioner to solve.

In any estimation of the value of protamine insulin one is forced at the moment to depend upon immediate results, such as prolongation of the action of insulin and freedom from reactions, but, beneficial as these are, we consider them to be insignificant in comparison to the better control of the diabetes which it makes practical. Formerly a diabetic could maintain a reasonably normal blood sugar for one-half, two-thirds, or three-quarters of the twenty-four hours, but consider what this signified if applied to the course of his diabetes throughout twenty years—the average duration of diabetes with onset in 1936. It would mean that for one-half to one-quarter of this period, namely, 10 to 5 years, he would be living with an abnormal blood sugar with all its implications. And it is this long-range view of the diabetic situation which is ultimately the more important.

“*The Hagedorn Era*”.—Whereas the three Banting Eras, early, middle and later, made increasingly possible the conquest of coma, the Hagedorn Era makes possible the approximation of the physiological processes of the diabetic so nearly to normal that arteriosclerosis should cease to be his distinctive enemy. Protamine insulin has broken the spell of content which the original insulin induced. Now we know improvements in insulin are possible. These are the chief reasons that for ourselves we think it only fair and a just due to the Copenhagen investigator to name this present era the “Hagedorn Era”.

The administration of protamine insulin is more complicated than regular insulin and various precautions are necessary for its successful use. Deliberately, however, we have taught our patients to employ it, and have had them carry out the mixture of the insulin with the protamine in their own homes, because if protamine insulin is to be used widely, patients must be able to make these mixtures themselves. It is true occasionally they have made gross and amusing errors, but it is a fact that in no instance have we felt compelled to change over our plans and arrange for the mixture of the protamine with the insulin in the hospital or office. Patients have been taught to keep the protamine insulin in the ice chest, to use only dry, cold, and sterilized syringes and needles, and when both old and new insulin are to be injected to make separate injections. In a few patients we attempted to employ a needle three-quarters of

an inch long and two dry syringes, injecting the old insulin first, then slightly withdrawing the needle and with a new syringe injecting the protamine insulin. This did not seem a practical method for most patients to carry out without obtaining an undesirable mixture of the two types of insulin in the tissues.

*Dosage*.—The number of units of protamine insulin required for a diabetic whose diabetes is controlled is not materially different from the number of units of regular insulin, no matter whether the protamine insulin is given in one or two doses. Protamine insulin acts so slowly that its full effects may not become manifest for five or six days, and herein danger lies, because the dose may have been increased so markedly as a result of heavy glycosuria that at the end of that period unnecessarily large amounts are being employed. Especially is one apt to obtain reactions at this time if old insulin and protamine insulin are combined before breakfast. It is so unusual for us doctors to expect our patients to have normal blood sugars early in the morning that a reaction may be precipitated if the patient receives quickly acting old insulin a half hour or more before his morning meal. Therefore, we have recently made it a rule that no patient taking old and new insulin should have it injected more than 30 minutes before taking food.

In changing from old to new insulin it is probable that in the controlled case approximately the same number of units will be employed. For the first few days following the shift the glycosuria will increase, but eventually it will disappear and in a considerable number of patients the reports come back that the patient needs less rather than more total units than before the protamine insulin was started. By no means can this statement be made unequivocally.

*Diets*.—Protamine insulin works successfully even if the carbohydrate in the diet varies from 100 to 275 grams.

*The indications for the use of protamine insulin*.—1. A trial should be made with diabetics of recent onset, because it is probable that such patients can be controlled with a single daily dose of protamine insulin from the beginning of treatment. Indeed it is our impression that we will never learn what protamine insulin can do until we use it as a remedy *sui generis* and observe patients treated with it exclusively over a period of years.

2. High fasting blood sugar values are a definite indication, because of the great advantage to a diabetic in beginning his day with the nearly normal metabolism indicated by a normal blood sugar.

3. Multiplicity of dosage can be avoided by the use of protamine insulin, and the consequent gain in simplicity and convenience of treatment improves the end-results.

4. Sensitivity to insulin, as indicated by the frequency of reactions, constitutes the fourth major indication.

5. Hepatomegaly is an indication, because of the reported efficacy of protamine insulin in reducing the size of the liver (Hansen).

6. Lipodystrophy may be favourably affected by the reduced number of injections and lessened acidity of the preparation.

7. Finally, it may prove to be of especial value in mild diabetics, in patients with hyperlipæmia, cardiac cases in whom hypoglycæmia should be avoided and, for the same reason, where there are occupational hazards.

#### CONCLUSION

With protamine insulin the fundamentals of treatment of diabetes are not changed, but the

ideals of treatment are more nearly achieved. Diabetes today is a disease to be respected, and neglect to do so spells disaster. Diet and exercise are as essential as ever. The patient must not overeat, but it seems likely that having determined the insulin dosage for a given quantity of carbohydrate the protein can be determined by adjustment to the age and size of the patient, and fat regulated by body weight, and even the carbohydrate can vary 10 to 20 per cent up or down with comparative impunity.

The simplicity of the administration of insulin in one or two doses instead of two, three, or four doses will appeal so generally to patients that the probability is strong that the number of diabetics taking insulin will increase. As a result the percentage of deaths from coma should fall at an accelerated pace.

Best of all is the hint that the more complete control of the disease which the new insulin makes possible may so raise the standard of bodily health that the diabetic will be less subject to, and will resist more successfully, the various so-called diabetic complications, infections, vascular degeneration, and abnormal neurological and ophthalmological manifestations.

## PRESENT-DAY METHODS OF TREATMENT OF CARCINOMA OF THE BREAST: INDICATIONS FOR THE USE OF EACH METHOD\*

BY ROBERT M. JANES

*Toronto*

THE treatment of carcinoma of the breast remains a difficult problem. The results obtainable through the use of surgery or radiotherapy are only too frequently disappointing. An expression of opinion as to the place that each of these forms of therapy should occupy may be of some value. It is not possible or wise to form unalterable conclusions at the present time, since the technique of radium and x-ray therapy is constantly changing. Following a recent visit to Europe, a considerable survey of literature on the subject, and with the knowledge gained from the privilege of seeing all cases of cancer of the breast that have come to the Toronto Branch

of the Ontario Institute of Radiotherapy, I have attempted to formulate my views on the subject.

Cancer of the breast is always at one stage in its development a local disease, capable of being cured therefore by either complete removal or complete destruction of the local area. At a time, impossible to determine in any given case, the malignant cells wander away into the surrounding tissue spaces and subsequently into the lymph vessels in which they are carried to the nearest group of lymph nodes. The anatomy of the spread by way of the lymph vessels and lymph nodes is well understood, but one is perhaps less apt to remember the extent to which the cells may wander in the surrounding apparently healthy tissues. Dudgeon and Barrett<sup>7</sup> examined by means of the wet-film method the muscle, the skin and outlying parts of the gland in 37

\*From the Department of Surgery, University of Toronto, and the Ontario Institute of Radiotherapy, Toronto.

Read before the Surgical Section, Academy of Medicine, Toronto, on November 19, 1935.