1956

The Story of the history of diabetes mellitus

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Submitted in Partial Fulfillment for the Degree of

Doctor of Medicine

College of Medicine, University of Nebraska

March 31, 1956

Omaha, Nebraska

A DEFINITION OF DIABETES MELLITUS

"Diabetes is an hereditary disease, characterized by an increase in glucose in blood and the excretion of this sugar in the urine; it is dependent upon a deficient formation or diminished effectiveness of insulin secreted by the beta cells of the Islands of Langerhans of the pancreas and is functionally interrelated with conditions arising in the liver and in endocrine glands other than the pancreas particularly the pituitary and also the adrenal and thyroid."

--Elliott P. Joslin (1)

ACKNOWLEDGMENTS

Without assistance, guidance and encouragement, few accomplishments are possible. This is especially true when writing a paper. Dr. Mary Jo Henn, the author's advisor, has provided all three and it is to her that this paper is dedicated.

In addition, the author would like to thank Dr. Morris Margolin for the use of his private library and for his many valuable suggestions.

The author would also like to acknowledge the assistance given him by the staff of the University of Nebraska College of Medicine Library. Especially valuable was the help of Mrs. Bernice Hetzner, Head Librarian, who secured many articles and references for the author from outside sources. Thanks are also due Miss Marie Harvin, who kindly consented to read and edit this paper. But beyond this, it was the completeness and exceptional adequacy of the library that made a paper of this type possible.

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Foreword:

This paper will attempt to tell a story. A true story, but one without a final conclusion. The plot will follow the evolution of diabetic history and is divided into three sections: The Era of Observation, The Era of Starvation and the Era of Treatment. Each of these sections has its own particular cast but with all members concentrating on only one subject--the cure of diabetes mellitus. The particular contributions of each member of the cast will be discussed in relation to the definition of diabetes previously presented.

The author's division of the history of diabetes into three eras is quite similar to that proposed by Allen (2). However, it was propounded before reading the work of Allen and for the purposes of this paper it is completely satisfactory. It must be remembered that the three eras are interwoven, for there was treatment of diabetes in the earliest stages of its recognition in history. Today we still maintain our diabetic patients on diets.

The Era of Observation begins with the first known reference to diabetes as found in the Ebers Papyrus (3) in 1500 B.C. and extends to 1797 A.D. At that time, Rollo (4) introduced the first diet used in the treatment of diabetes and thus initiated the Era of Starvation.

This era prevailed until 1921 when Banting and Best (5) discovered insulin and introduced the Era of Treatment. It will be noted that the Era of Observation is greater than 3000 years in length, while that of the Era of Starvation is just over 100 years long; and that of our present era, the Era of Treatment, has proceded for a mere 35 years. Thus it would seem that we are elucidating the secrets of diabetes at an increasing rate. But, we cannot yet predict when we will enter the Era of Cure.

The construction of this paper is such that the author sincerely hopes the occasional reader will enjoy himself. The style is that of the author's. Levity is frequently used, rather then a mere statement and re-iteration of fact after fact. It is his feeling that history is living and should be treated as such. Finally, is should be stated that the primary purpose of the paper is not only to further the understanding of diabetes in particular but also, the evolution of modern medicine in general. That such an understanding can be obtained from a living thesis should be a tangible aid.

The Era of Observation: 1500 B.C. - 1796 A.D.

"Oh, most high and exalted priest, communicator with the gods, most devine in thine own right, producer of good spirits and creator of miraculous drugs, give to me something with which I might control the excess flow of urine that has been upon me since twenty rising suns after the flood of the might River Nile."

This beseechment of a priest by a patient suffering from diabetes might have been heard in ancient Egypt prior to 1500 B.C. At that time a priest recorded the methods of diagnosis and treatment for various illnesses. This record is known to us as the Ebers Papyrus (3). It has in its annals the diagnosis of polyuria, which Barach (6) and Major (7) tell us alludes to diabetes. With such a stirring and passionate appeal, it was quite impossible for the priest-physician to refuse to prescribe some remedy which might aid the patient. Such an elixir vitae might be this (3):

"Remedy to Regulate the Urine

A-measuring-glass-filled-with-Water-from-the-Bird-pond	1
Elderberry	1
Fibres-of-the-asit-plant	1
Fresh Milk	1
Beer Swill	1
Flowers-of-the-Cucumber	1
Green Dates	1

Make into one, strain, and take for four days."

It is not known whether this rather unpalatable concoction had the desired effect, but it can be assumed that the patient was aided in his progress towards acidosis by the emetic action of the remedy. Bryan stated (3), "The less said about the remedies for the treatment of Polyuria and frequency of Micturition the better." Regardless of the manner of treatment, proper credit must be given to these ancient peoples for recognizing this so-called disease of polyuria. There are apparently no other known records of the disease for the next fourteen and one-half centuries.

Hippocrates (6), in the early Greek Era, 460-377 B.C., neither recognized nor recorded the sign polyuria or the disease diabetes.

There is no further note of this disease until the time of Christ. Aulus Cornelius Celsus then accurately described diabetes (6), writing of it as a disease with polyuria and wasting (8). He was so impressed with the quantity of urine produced that he stated that the patients thus afflicted had a discharge of urine greater than the amount of fluid taken by mouth. This statement was to stand for 1500 years before being discounted.

In the Late Greek Period, 200 A.D., there lived a man of some eminence medically. He was Aretaeus, the Cappadocian. His descriptions of diseases were and still are notably accurate, being based on what he could see, what he could feel and what he could hear. An English translation of his description of diabetes will be given (9):

"Diabetes...being a melting down of flesh and limbs into urine. Its cause is of a cold and humid nature as in dropsy. It affects kidneys and bladder, the patients never stop making water. It takes a long period to form (the disease) but the patient is short lived if the constitution of the disease be completely established. Thirst unquenchable. More water is drunk then is passed in urine. If water is not given, they expire rapidly (at no distant turn).

If they restrained themselves from passing water, they become swelled in loins, scrotum and hips. When they give vent they discharge the collected urine, and the swelling subside for the overflow pass to the bladder.

If early, thirst is not marked, but patients have parched mouth, while frothy saliva. Little more then normal urine is passed. A sensation of heat or cold from the stomach to bladder is the advent of the approaching disease.

Emaciation seen with progression of the disease.

The disease appears to me to have got the name diabetes, as if from the Greek word which signifies a siphon, because the fluid does not remain in the body, but uses man's body as a bladder whereby to leave it.

Cause of the disease is either a preceding acute disease, or some lurking malignity. It is also similar to a condition produced by the bite of a dipsar (a viper).

Treatment: Species of dropsy differing only in the place by which the humour runs. In ascites, receptacle is peritoneum. In diabetes, kidneys and bladder. Thirst greater in the latter since fluid runs off.

The thirst must be cured for as water is taken and passed off, in the urine, particles of the body are also carried away.

Strengthen the stomach since it is the fountain of thirst. When you therefore have purged the hiera, use as Epithemes the nard, mastich dates, and raw quinces. Taken they form a cataplasm. Water must be boiled with autumn fruit. Eat on milk and cereals. Astringent wine gives tone to the stomach. Do not dilate since they clear away other humours."

We can see that Aretaeus recognized polyuria, polydipsia, emaciation, the rapidity of death with an uncontrolled case, the early symptoms of parched mouth and the normal appearing urine. Also, could a more appropriate name have come to the Greek physician than one which signifies a siphon? It will be noted that Aretaeus recognized the fact that more water is drunk then is passed, but the word of Celsus is the one that appears in later literature.

At approximately the same time, the great Galen noted that diabetes was a "weakness of the kidneys which cannot hold back water" (6), and that the urine had the appearance of unchanged drink. Thus the great Galen whose works so influenced and limited the medical thinking of Europe in the subsequent centuries felt the disease to be worthy of little mention. Could it have been because he could do nothing for it, or was it because he saw so little of the disease he felt it to be rare?

From the Mediterranean area, which was about to be plunged into darkness and ignorance for several centuries, we move to the older civilizations of the Orient. There we find a reference clearly describing diabetes and its peculiarities in the Second Century A.D.

> "In Pramelia, or polyuria...caused by air, there is flabbiness of the flesh...dryness of the throat, sensation of sweetness in the mouth, burning of the palms and the soles, and attraction of ants by the urine."
> "When the urine is seen to be limp and is as sweet as honey...and the tissue are greatly attenuated, the disease should be regarded as having the excited air for its cause."

The preceding quotation is found in the writing of the Hindus as noted by Major (7); but according to Barach (6), another reference is found from the same peoples in the sixth century. At this time the disease was called Madhumeha, honey urine.

> "It is a disease of the rich and one that is brought about by the gluttonous over indulgence in rice, flour and sugar. The order of disease is ushered in by the appearance of morbid secretion about the teeth, ears, nose and eyes. The hands and feet are very hot and burning, and the surface of the skin is shining as if oil had been applied to it. This is accompanied by thirst, and a sweet taste in the mouth. The different varieties of this disease are distinguished from each other by the symptoms of deranged humours and by the colour of the urine. If the disease is produced by phlegm, insects approach the urine, the person is languid, his body becomes fat and there is a discharge of mucus from the nose and mouth, with dyspeptic symptoms and looseness of the skin. He is always sleepy, with cough, and difficult breathing.
> ...2. The urine is like the juice of the sugar-cane in colour and taste. ...8. When there is a copious secretion of urine which is sweet and cold. 9. When there are frequent calls to make urine, which is discharged in small quantities...."

Yet another reference alluding to the sweetness of the urine was made in 500 A.D. by Susruta, an Indian physician (8).

It was also known at this time that all the hereditary and congenital forms of the disease were incurable, and that if other forms were not properly treated, they generally terminated in sweet urine. With the appearance of this latter sign, the disease became incurable (6).

The Chinese and Japanese, as recorded in 229 A.D. (6), wrote that urine of diabetics was large in amount and was imbued with such sweetness that it attracted dogs. Furunculosis was also noted to be associated with the disease.

Arabia is the site which produces the next notable recording of the recognition of diabetes (6). Avicenna (8), during the eleventh century, claimed that diabetes may be primary or secondary to another disease and also observed that diabetic patients have irregular appetites, suffer great thirst, nervous exhaustion, an inability to work and loss of sex function. He also described "bronze diabetes." He noted that urine leaves a residue like honey and that carbuncles, phthisis and diabetic gangrene were often seen. He stated that treatment was not effective.

In the records of the Oriental and Arabian peoples, written during Europe's Dark Ages, we find that they knew of the heredity, the glycosuria, the polyuria, the association with infection, the relationship with carbohydrate rich diets, the dehydration, the dyspepsia, the lethargy and deep breathing associated with acidosis, the neuropathy and the apparent incurability of the disease.

The Renaissance spread gradually over Europe. Its gestation period was two centuries, give or take a few decades. The "re-birth" of medicine was not so leisurely, particularly in Germany.

Galen's views, which had permeated the thinking of medicine for many centuries and had withstood the test of a non-corrosive type of time, were the alpha and omega of medical science. During the early part of the sixteenth century a bombastic, egotistical, inflated, bellicose mass of cornified protoplasm answering to the name of Aureolus Phillipus Theophrastus Paracelsus Bombast von Hohenheim, better known as Paracelsus (6), appeared on the scene. Being amont the most radical of the heretics, he gave medical lectures in German instead of Latin, he denied the theory of the "Four Humours" and permanently desecrated Galen by burning his books. Paracelsus was among the first to record his views on the disease diabetes. He evaporated urine, obtaining "salt" which he stated made the kidney thirsty and caused polyuria. Although he was subsequently proved wrong on all points mentioned, this man's attributes extended far beyond his feelings on diabetes. As was fitting with his life, Paracelsus died after he was pushed from a window during an argument.

From the time of Paracelsus the number of references to diabetes in the literature increase. This increase is directly related to the popularity of the printing press, which made its appearance in the fifteenth century under the guiding hands of Johann Gutenberg. Thus it became possible for the learned men, and those not so learned, to spread their knowledge by means of the printed page.

Shortly after the recordings of Paracelsus, Cardano (6) dispelled the idea of greater fluid output than intake by the remarkable method of keeping a record of the intake and output of patients with diabetes.

In view of the knowledge of the age, Trincavella (10) offered a rather remarkable solution to the problems of diabetes. He pointed out that the urine was composed of unaltered fluid ingested by the subject, since it possessed the taste of medicinal drinks taken by the patient. Hence diabetes resulted from the intake of sweet drinks containing sugar in excess.

Thomas Willis (1621-1675) is generally credited with the heroic discovery that the urine of diabetic patients is sweet (11). Although he was preceded in this discovery by many authors, no glory should be diverted from this man for he brought this fact to the attention of his contemporaries. Writing in Latin, Willis states in Section IV, Chapter III of his Pharm. Rationalis (12):

"Of The Too Much Evacuation By Urine And its Remedy; And Especially Of the Diabetes Or Pissing Evil, Whose Theory And Method Of Curing, Is Inquired Into."

"The Diabetes was a Disease so rare among the Ancients, that many famous Physicians have not som much as mentioned it and Galen never knew above two that were troubled with it; but in our Age, that is given so much to drinking and especially to guzzling of strong Wine, we meet with very frequent, not to say daily examples and instances of this Distemper.

...But as to what several Authors say, that the Drink is little or nothing changed, there is no truth in their assertion: because in all People...their Urine was very different, not only from the Drink that they took in, but also from any other humours that are usually generated in our Bodies, being exceedingly sweet, as if there had been Sugar or Honey in it."

Willis further expounds on the clinical picture. He also presents his view that this disease is not primarily in the kidneys but is an affection or distemper of the blood, sharing the cause with "nervous juice." He also recognized the presence of neuropathy by stating,

"...I have observed in many People who have been subject to this disease by intervals, that a little before they fell into such a flux of urin, they felt flying, running pains through their Bodies, and corrugations sometimes with dizziness or stinging, and other while with frequent contraction or convulsions, twingings of the tendons and other disturbances and restlessness of the spirits; which was a certain sign that the liquor which moistened the nervous fibers, being degenerated from its temper, and filled with dregs, did irritate or provoke the spirits, and force them into disorders."

Reaching no definite conclusion from the clinical picture he raises the question, "Why it (the Urine) should be so wonderfully sweet like Sugar or Honey is not easie to untie."

The following prescriptions were ones prescribed by two men which whom he consulted, of which he said, "... they had prescribed the following remedies by the use of which he (the Patient) seemed to grow well again."

> "Take of the Tops of Cypress viii handfuls, of white of Eggs beaten together, two pints, of Cinamon ℥ ss, when you have cut them small, pour to them of new milk vii pints distil them in common instruments, taking care that it burn not; and let the patient take ℥ vi thrice a day."

and

> "Take of Gum Arabick, and Gum dragant each ℥ vi of Pened ℥ i make a Powder and let him take about ℥ i or ℥ iss with ℥ iii or ℥ iv of distilled water."

From the above remedies, it seems that little therapeutic progress had been made from the time of the Ancient Egyptians. They had, however, two aspects in common: 1) Both were singularly ineffective; and 2) both were unquestionably vile and repulsive.

The year 1682 marked a failure for the process of serendipity and also placed the title of unconciousness upon a great physician. This was the year that Brunner depancreatized a dog in an effort to determine if the pancreas were necessary for digestion (13). Brunner felt that the duodenal glands he described associated with Peyer's Patches were the only necessary elements for digestion in the gastro-intestinal tract. With the dog depancreatized, it was noted that the animal made water frequently and displayed a marked thirst. The frequency of his urination was not at the expense of the total volume at each urination. The dog apparently delighted Brunner by snatching meat from a meat market where he had once been kept. He concluded that the dog in no way suffered in health. According to Macleod (13) this experiment depressed further investigation in the pancreas for 150 years.

In the eighteenth century, Home (7) was the first to point out that yeast fermented the sugar in diabetic urine. Mead (10) in 1754 restated that diabetes was independent of the kidney, while in 1763, Sauvages (10) described seven kinds of diabetes. During this same period, Cullen (11) added the adjective "mellitus" from the Greek word mel-itoes, meaning honeyed or sweet, to distinguish the disease from "insipid" diabetes. Dolseux (10) in 1775 pointed out that the blood serum of diabetics possessed a taste of sugar, thus proving that sugar in the urine was not formed in the kidney. One year later, Dobson (6,7,8) demonstrated that diabetic blood is sweet and diabetic urine contains fermentable sugar. Shortly after this, Cawley (6) diagnosed diabetes by demonstrating the presence of sugar in the urine, instead of from symptoms and signs alone. According to Macleod (13), Cawley was the first to suggest a relationship between diabetes and the pancreas. The type of relationship is unknown.

The Era of Starvation: 1797 - 1921

The treatment of diabetes in this era might be termed "dietary control." However, the various methods amounted to nothing more than starvation. As we shall see, the life of the patient generally varied directly with his ability to starve himself. Although life expectancy was increased with this treatment, the disease remained incurable. Death prevented further starvation after no more then a few years and at times the patient succumbed in a matter of months.

Two segments of science run parallel to each other during this period. The clinicians attempted to control diabetes by means of diets and other methods, while the researchers were mainly interested in the etiology of this disease--stressing the disease and not the patient. In the former group we find Rollo, Bouchardat, Cantani, Naunyn, Külz, von Noorden, Joslin, Allen and many others. In the latter group we find Bernard, von Mering and Minkowski, von Fehling, Benedict, Langerhans, Opie and others. These two groups will be considered separately in the following discussion.

Mighty England of the later eighteenth century produced a medical heretic. Rather then dunking him in the river for witchcraft as the newly freed American Colonies were doing, they let him write a book. From what was written, it can be seen that this gentleman had two unusual patients with which to work. These two patients were found in the army in which John Rollo served as a physician. After all, where else could human guinea pigs be found?

Aside from this, Rollo (4) gave to the medical profession the first rational method of treatment. This was the first great advance in treatment in the history of diabetes. Diagnosis of frank cases of the disease was not difficult and proof of sugar in the urine of diabetics had been offered (6,7). The basis for his dietary treatment can best be given in his own words:

"1. Diabetes mellitus is a disease of the stomach.
2. The kidneys, other parts of the system, and head and skin are secondarily affected.
3. The stomachs actions consist in an increased action and secretion.
4. The cure is accomplished by regimens and medicines preventing sugar formation.
5. Abstinence from vegetable matter, with a diet of animal food, with emetics, hepatified ammonia and narcotics, comprehend the principal means to be employed.
6. Two objects occur in cures: 1) relieve increased action of stomach; 2) prevent sugar formation vegetable matter.
7. Lungs and skin have no connection with production of the disease.
8. Quantity of urine is proportional to water taken in.
9. That diabetes mellitus is so far understood, as to be successfully cured."

His series of two cases did show remarkable relapses. The price to be paid was one of taste in which the diet consisted of meat--rancid, repulsive, repugnant, moldy meat. This was a price not paid by most patients.

His first patient's urine remained clear of sugar as long as he was on this diet. (It should be noted that the present day tests for urinary sugar were unkown. Instead, the daily secretion of urine was boiled until a thick syrup was formed. This syrup, if sweet, was considered as evidence of sugar in the urine and if not sweet, of being free of sugar.) After several weeks of therapy, during which time no sugar was found in the urine and during which time the urinary volume decreased markedly, the patient was dismissed as cured. The second patient would not follow the diet prescribed and slipped from the care of Dr. Rollo. He died at a later date. It should be stated that his cardinal symptoms of polyuria, polyphagia and polydipsia were alleviated during the time he was on the near starvation diet of his physician.

One devotee' of Rollo was Robert Watt (2). Writing in 1808, this man not only advocated Rollo's diet, but carried it one step further by stating,

> "The antimonial powders appeared to have a more decided effect. They produced very severe sickness, vomiting, and commotion in the stomach and bowels. The night after taking these, the urine was greatly reduced, and next day he found himself uncommonly well. On repeating them, they had not such violent effects, nor was the relief obtained so decisive.... Anything which produces sickness has a temporary effect in relieving diabetes, by diminishing the quantity of ingesta."

He also stated,

"...the first aim of the practitioner should be to remove a portion of that food, which since it does not nourish, must oppress and injure the system. Animal diet accompolishes this object to a certain extent...."

It was observed that feeding the patient with diabetes in an attempt to enhance his strength was without reward, while starving him produced some desirable effects. Bleeding and blistering were also adhered to by this practitioner.

Yet another physician, Pelham Warren (2) supported Rollo but gave dietary management a secondary place in the treatment of diabetes, feeling that opium was the primary therapeutic agent to be used. It is believed that he was the originator of the opium treatment of this disease. The fact that opiates tend to decrease the appetite was not recognized at this time.

Prout (2) also recommended a diet but only for the reason of not overloading the stomach. He felt that vegetables could be allowed in the diet.

The four previously mentioned men were the chief supporters for dietary treatment at this time--a regimen to be ignored for the following 30 years.

Although the site of the disease was erroneously placed, we have patients who were helped by dieting. But as is often seen in medical history, the medical profession was not yet ready to accept a method of treatment without further evidence of its effectiveness. This is an amazing method of suppressing that which is new, since further evidence cannot be gained without trial and if the profession will not try it, the treatment dies. Therefore, dietary treatment fell on its unpalatable face for many years and diabetes continued to wend its unaltered course through the human race.

The therapeutic measures used by the practicing physician from the early to mid-ninteenth century are well stated by Basham (17). Permanganate of potass, sulphite of soda, hydrochloric acid, opium, diaphoretics and alkalies were tried, all with singular and resounding failure. Basham felt that opium was of some benefit, since it relieved the patient subjectively. In the light of knowledge at this time, the rationale for these drugs was quite good. The basic assumption was

> "Diabetes is a disorder of the digestive and assimilative functions.... The alimentary principles are more rapidly converted into sugar or glucose than in healthy digestion."

With this in mind, permanganate of potass was used to supply oxygen in order that glucose might be broken down into smaller particles in the intestine. "Diaphoretics (antimonials, warm baths) increase skin secretion of fluid and thus lessening the load on the kidneys." It can be seen that the faulty reasoning was based on inaccurate knowledge of glucose metabolism. This clinician made no mention of dietary restriction.

It was the middle of the ninteenth century before more was heard from those interested in diet as a means of treatment in diabetes. The leader of this minor renaissance was Apollinaire Bouchardat.

Bouchardat (18) was a man well fitted for the leading role which he played in the advancement of diet as the treatment of diabetes. His vivid imagination gave birth to many of the basic concepts of dietary treatment. However, it was Rudolph Eduard Külz (2) who proved many of Bouchardat's suggestions, thereby putting them on a scientific basis. Bouchardat gave hope to diabetics. This he did by dietary control, much after the fashion of Rollo. He felt that glycosuria had its origin in the sugar of the blood, which in turn came chiefly from carbohydrate in the diet. He urged that his patients regulate their carbohydrate intake, although recognizing that protein could be converted to glucose. His success with diets lay in the fact that the epicurean senses of the patients were satisfied with not-unsavoury foods. Bread and milk were wholly excluded, but gluten bread was allowed. (This bread was low in carbohydrate. Later it was proved to be ineffective, in that it contained a significant number of utilizable calories. Occasional fast days were utilized to supplement the diet restrictions.

In addition to diet, Bouchardat was among the first to suggest an influence of the pancreas in the etiology of diabetes and was the originator of attempts to produce it by pancreatectomy in dogs (2). He based his reasoning on the fact that the pancreas of diabetics was often found to be atrophied. This atrophy with the preceding hypertrophy of the stomach was felt to be the seat of diabetes. His attempts at pancreatectomy were without success.

Using the process of fermentation, Bouchardat demonstrated that the blood of diabetics contained sugar in amounts which could not be found in normal blood. He recognized the difference in action between glucose and fructose, employing the latter as a sweetning agent in his diet (2, 18).

Arnaldo Cantani ably supported the concepts of Bouchardat in the latter part of the ninteenth century. Latitude in diet was disallowed, the patients often being placed in locked rooms for several weeks and fed on a completely carbohydrate free diet (2). Up to 500 gm. of meat was given daily. As Bouchardat before him, Cantani proposed moderate exercise as being beneficial to the diabetic patient and recommended such for his patients (19). The support of the dietary regimen was Cantani's main contribution to the therapy of the disease. He advanced the theory that there was an abnormal or "paraglucose" present which could not be used by the body. He felt that any atrophic changes in the pancreas were the result rather then the cause of diabetes.

The man succeeding Bouchardat and carrying on the work of promoting dietary treatment was Bernhard Naunyn. This German stood alone in his country as a proponent of this treatment. Although he was not known for his great discoveries, Naunyn was an exceptional clinician and trainer of men. We shall hear later of his students, especially Minkowski (20).

To Naunyn goes credit for humanizing dietary treatment, since he felt that individualization was necessary. He realized that a person in a sedentary occupation required fewer calories then one engaged in heavy labor. He placed food intake on a caloric basis. He did not connect the disease of diabetes with the pancreas, supporting instead the idea that diabetes was a functional deficiency in which treatment had to be directed toward sparing the weakened function. According to Allen (2), he also considered that "It is certain that disease of the nervous system and of the pancreas can produce diabetes." Although he limited carbohydrate and protein intake, he felt that the sugar formed from fat was negligible and that this substance could be plentiful in the diet, if total dietary intake was maintained below 35 cal/kg. (6). His plan of treatment

(2) was to withdraw carbohydrate gradually, to give alkali if the patient were acidotic, and to limit total caloric intake with about 125 gm. protein in the daily diet. Exercise in limited quantities was also advocated as helpful.

Marsh, 1854, and Külz, at a later date, supported diet as the only means to control diabetes (2). The latter author was the first to calculate diets on the basis of calories.

von Noorden (2) was the next great leader to adhere to dietary treatment. He advocated the regimen of Külz--that diet in which carbohydrates were restricted. His main contribution was that of continuing the use of this therapy. He advocated the "oat cure" at one time, believing that oatmeal was a source of bulky, low-calorie food. Further study failed to support this treatment. This cure ranks with that supported by Donkin (21) in which diabetes was cured by feeding the patient a diet of skim milk. Also seen during this period (later ninteenth century) were the rice cure, the potato cure and various bread cures (2).

Guelpa (2) with his purgation and starvation, Petren (7) with his low protein, high-fat diet, and Woodyatt (2) and Joslin (22) following a fasting regimen were all supporters of dietary therapy preceding the last of the great dietary clinicians.

The author of the last great dietary method was Frederick Allen. This author's voluminous work, published in 1913 (23) and followed by a monograph in 1919 (2), was the final word on dietary treatment. Basically, as with many of the other diets, Allen's plan of undernutrition or planned starvation was one which consisted of total dietary regulation. The patient was limited to approximately 30 cal./kg./day with little more then 30 gm. of carbohydrate per day in a case of moderate severity. Protein was limited in ration to the severity of the diabetes, while fat was added to bring the total diet to the necessary caloric value. Patients were regulated in the hospital, receiving instructions on plannming their meals and preparing their foods. If a sugar free state were obtained, a sugar tolerance test was generally given to determine at what level the patient could be maintained. As an integral part of the therapy, fasting days were instituted, during which the diet was limited to beef-stock broth and other low calorie liquids. Even if the patient were relatively well controlled, it was not unusual to have a fasting day every two weeks. Fasts were maintained up to 30 days, if necessary to obtain sugar free urine. This therapy was the epitome of planned starvation. In spite of the severity of the diet, the patient's life was usually lengthened although the prognosis remained poor.

Let us turn back to the early years of the ninteenth century and follow the developments in basic and applied research up to this point.

We find that Latham (2) in 1811 and Gregory (2) in 1825 further established that there were two types of diabetes--mellitus and insipidus. This substantiated the idea that glycosuria was necessary for the diagnosis of diabetes. This theory was also supported by Chevruel (10) who showed that the sugar in urine and grape sugar were identical, that is, both glucose. Advances in this direction were supported by the discovery of Tiedemann and Gmelin, in 1821, that sugar formed independently of carbohydrate taken into the digestive tract (10). The year 1833 provided two steps which broadened the understanding of diabetes: Stadelmann (6) discovered B-oxybutyric acid and recognized that diabetic coma was the result of the increased formation and accumulation of this acid; and Richard Bright (13) suggested that there was a relationship between diabetes and the pancreas. But the relationship was not explained.

An important step in the early diagnosis of diabetes was taken in 1841 with the announcement of Trommer's discovery of a copper reduction qualitative test (2) for glucose and other reducing substances. This was followed in 1848 by the quantitative method of Fehling (14,6). Another three-quarters of a century was to pass before significant advances were made in these tests.

During this period, Claude Bernard (16) contributed much to the understanding of carbohydrate metabolism: the discovery of glycogen as produced by the liver, the finding of glucose in the urine following a pin prick of the floor of the fourth ventricle of the brain--his piqûre experiment--and many others not related to diabetes. He felt that diabetes was a permanent form of piqûre in which the brain stimulated the release of glucose by increasing blood volume going to the liver where endogenous blood ferments could act on the glycogen (2). He also felt that the pancreas could not be removed and leave a living animal. The cause of death in those that survived the pancreatectomy was extreme emaciation in spite of a voracious appetite (16). Bernard had missed the diagnosis of diabetes.

For twenty years, Bernard continued his work on basic physiology. Others were working on the metabolism of sugar and on the cause of acidosis and of coma. Among the men who made important contributions in this field were Ferichs (14), Naunyn (2), Magnus-Levy (14), Pavy (2) and many others. The authors to be mentioned below made some of the more remarkable discoveries.

In 1874, Kussmaul wrote of a hitherto undescribed terminal symptom complex which he called "diabetic coma." The striking features were noted to by dyspnea of a special character associated with rapid pulse and general debility

(23). He felt that the dyspnea was due to an intoxication resultion from the chemical metabolic disorder in diabetes. Although Kussmaul was commonly credited with the initial description of diabetic coma, it was Stadelmann (6), in 1833, who discovered B-oxybutyric acid and recognized that diabetic coma resulted from the increased formation and accumulation of this acid. Naunyn (6) and Minkowski (7) many years later also worked with B-oxybutyric acid. Naunyn felt that both acetonuria and diaceturia were part of the acidosis and both originated from that acid. He is credited with coining the term "acidosis." Petter (6) in 1857 was one of the first to discover acetone in diabetic urine. Thus in the last half of the ninteenth century it was felt that these products of incomplete metabolism were the cause of acidosis and coma.

During this same period, there developed more and more evidence condemning the pancreas as the villain that caused diabetes. Many authors noted gross lesions of the pancreas at post mortem examination. Allen (2) lists such men as Cawley, Bright, Bouchardat, von Recklinghausen, von Ferichs, Cantani and Lancereaux. The increasing frequency of these reports gave weight to this relatively new concept. Lancereaux and Lapierre (2,6) reported the sudden onset of the classic signs of diabetes in a patient who was later found to have an acute pancreatic lesion.

Adding to this evidence was the description by a 22 year old scientist (24) of islets of tissue scattered throughout the pancreas (13). In 1869, Paul Langerhans described these islets. But not until 1893, when Laguesse (8) gave the name of Langerhans to the islets, was he recognized for his important discovery (25).

In 1889, Oscar Minkowski (25), working in the clinic of Naunyn, accepted what amounted to a dare. Realizing that the great Claude Bernard had been unable to perform a successful pancreatectomy, he accepted the challenge of Joseph von Mering that he could not do it. Borrowing a dog from von Mering, he proceded, with the brashness of his 31 years (24), to extirpate the pancreas without difficulty. von Mering had left on a trip shortly after assisting Minkowski in the successful operation. Minkowski kept the dog about his laboratory as a pet. Within a few days he noted that the dog urinated frequently. He reprimanded the janitor for being lazy and forgetting to let the dog out. Subsequently, the urine was tested and found to contain sugar. Thus it was that the etiology of diabetes was found through serendipity. Fortunately Minkowski had the ability and training necessary to follow through this unexpected revelation. A lesser man might have missed this implication of polyuria. Although von Mering had done little of the work, Minkowski shared with him the credit of the great discovery, but by mutual agreement he carried on further investigation alone.

With the pancreas pointed out as the seat of diabetes, there was a great nodding of heads among those who had noted pancreatic lesions. Also, there was a great rush to hop on the pancreatic bandwagon. The band wagon was so effective that within the next 35 years a great many advances were made toward elucidation some of the secrets of diabetes, and the elusive secretion of the pancreas was sought with progressive zeal.

Many attempts were made to feed raw pancreas to patients with diabetes. White (26) presented two patients, who after having their diabetes evaluated were fed raw sheep pancreases--flavored with pepper, too. Following this experiment a liquor pancreaticus was injected twice a day. Both the experiments failed completely. Other attempts at this time met with a similar fate.

Eugene C. Opie was the first American researcher of note to enter the diabetic field. His study of the islets of Langerhans remains one of the classic works of the early twentieth century. Quotations from two of his articles clearly illustrate the extent and value of his work (27, 28).

> "In the production of glycosuria many factors doubtless take part, and in the present immature knowledge of carbohydrate metabolism, it is

impossible to maintain that diabetes is always caused by disease of the pancreas. A relationship has been observed between lesions of the islands of Langerhans and the occurrence of diabetes mellitus. In one of eleven cases of interlobular pancreatitis diabetes of mild intensity occurred. The sclerosis, which in this case followed obstruction of the ducts by calculi, was far advanced and affected the islands of Langerhans. In two of three cases of interacinar pancreatitis, diabetes was present--Hemachromatosis in the third. In a fourth case of diabetes, hyaline deposit between the capillaries and the parenchymatous cells had so completely altered the islands of Langerhans that they were no longer recognizable."

The conclusion of a later article is given below (28):

> "In the pancreas which has been described in this article, a lesion of obscure etiology has destroyed the cells of the islands of Langerhans, while those of the secreting acini, as well as other organs, are unaffected. The most successful experiment could not more accurately have selected these bodies. The association of diabetes mellitus with this lesion affords, I believe, convincing proof of the inference drawn from the preceding series of cases.
>
> ...Since diabetes is absent when, as the result of duct obstruction, the secreting portion of the gland undergoes great alteration, though the islands are spared, the conclusion is justified that it is those structures which influence carbohydrate metabolism."

Opie further noted that the intimate relation of columns of epithelial cells to a rich capillary network suggested that they furnish some substance to the blood--the hypothetical internal secretion of the pancreas. He noted that work by von Mering and Minkowski, Laguesse, Shäfer and Diamer pinned this substance to the pancreas and more specifically to the islets of Langerhans. He also reported Ssobolew's statement that after feeding animals with carbohydrate in considerable quantity, the cells of the islands become more granular than usual. Ssobolew also found that chronic interstitial pancreatitis, which in dogs follows ligation of the pancreatic ducts, spared the islands of Langerhans; this fact, he thought, explained the absence of glycosuria.

Although Opie was not the first to suggest that the elusive internal secretion of the pancreas controlled carbohydrate metabolism, his work did much to extablish this feeling. Others who worked in this field both before and after Opie were Sharpey-Schafer (6), Ssobelow and Schulze (6), Lemoine and Lannois (10), MacCallum (14) and Laguesse (30).

Laguesse (30) was the first to propose the concept of "enocrine secretion" as applied to the islands of Langerhans. His experimental work ably supported this concept.

MacCallum (29) performed experiments in America similar to those in Europe during this period. He partially pancreatectomized dogs, finding that after the operation they had a decreased tolerance to sugar. They not infrequently developed diabetes. He noted that ligation of the ducts of the remaining part did not change to status of the diabetes. This duct ligation caused atrophy of the acinar tissue of the pancreas, but the islands of Langerhans were intact. He concluded that there was a substance elaborated by the islands which controlled carbohydrate metabolism.

Similar results were obtained with the same procedure and also by simple duct ligation by Laguesse (13), Ssobelow and Schulze (6), Vassale (6), Sandmeyer (10) and Visentini (10).

Since many research laboratories elucidated a definite but unidentified secretion from the islets of Langerhans, it is not unexpected that many persons would administer pancreatic compounds and extracts to patients to control their diabetes. The most successful of these early attempts was that made by Zuelzer, Dohrn, and Marxer in 1908 (6,7,13). These workers prepared an alcoholic extract of adult ox pancreases which would reduce hyperglycemia. Even though there was some active principle in this extract, called "Acomatol," the reactions, both systemic and local, were so severe that administration to humans was abandoned.

Work continued in an attempt to isolate this mysterious substance. That it was still present was further shown by Clarke (13) in 1921. He found that a perfused pancreas yielded its hypoglycemic factor to the perfusate, thus proving that the internal secretion was still in the pancreas and that it had not run away.

During this period, Folin (31) and Benedict (32) wrote of their tests for determining reducing substances. Both tests were valuable assets in ascertaining the status of the diabetic patient. These tests were the first such advances in 75 years.

We find the status of the patient in 1921 not too enviable. The major difference between the patient of this time and that before Rollo's time is that the present patient died at a slower rate. It is not that he lived longer, but that he died slower. To tell a patient that he had diabetes was to sentence him to death. There was little hope for a diabetic. But in laboratory circles, the feeling was one of urgency, of watchful waiting and of expectancy. Those working with diabetes knew that the pancreas contained this hypoglycemic agent and it was only a matter of time until it was isolated. How long, no one knew, since the greatest minds dealing with the problem had failed. With this in mind, we enter the next era.

The Era of Treatment: 1921-

> "The hypothesis underlying our experiments was that the usual extracts of pancreas do not satisfactorily demonstrate the presence of an internal secretion acting on carbohydrate metabolism, because this is destroyed by the digestive enzymes also present in such extracts. To circumvent this difficulty we have taken advantage of the fact that the acinous, but not the insular cells, become degenerated in 6-10 weeks after ligation of the ducts.
>
> A fairly neutral acid extract of the degenerated gland, kept at a low temperature, was therefore prepared and its effect on the pancreatic diabetes investigated. Ten weeks after ligation of the pancreatic ducts the degenerated gland was removed and extracted with ice-cold Ringers solution. This extract injected intravenously or subcutaneously invariably caused marked reduction of the percentage of sugar in the blood and the amount of sugar excreted in the urine. Extracts of liver, spleen or boiled extracts of degenerated pancreas have no effect.
>
> Further investigations have shown the following: a, incubation of the extract, in alkaline reaction, for 2 hours, with pancreatic juice removes its effect; b, glucose given IV or per os is retained by diabetic animals if adequate dose of the extract are also administered; c, the clinical condition of the animal is improved by the extract; d, hemoglobin estimations before and after administration of the extract are identical; e, neutral extract kept in cold storage retains its potency for at least seven days; f, subcutaneous injections have a less rapid but more prolonged effect. Rectal injects are not effective.
>
> The experiments have been repeated on ten animals several of which were under observation for over two weeks." (5)

With this brief statement given before the American Physiological Society, Frederick Banting and Charles Best told the world of their brilliant discovery. The fascinating story of this discovery will be briefly given.

In November of 1920, Banting read an article by Moses Baron (33,34) which discussed the relation of the islets of Langerhans and diabetes, and emphasized those cases with pancreatic lithiasis. Baron noted that as long as the islets were not damaged following a duct calculi, diabetes did not result. However, if the islets were damaged, diabetes ensued. Banting had read this article in connection with the teaching he was doing at the University of Western Ontario Medical College. He had previously read of the work of Minkowski, of Langerhans, of Laguesse, of Zuelzer and of Claude Bernard as well as many others. After retiring for the night following his study of Baron's paper, Banting arose to write the statement: "Ligate pancreatic ducts of dogs. Wait 6-8 weeks for degeneration. Remove residue and extract (33,35)." Receiving moral support from his superiors at the medical college, Banting traveled to his alma mater, the University of Toronto, to see J.J.R. Macleod, one of the foremost authorities on carbohydrate metabolism. Canadian weather at that time was broiling compared to the reception and assistance Banting received from Macleod. The refusal could not have been more definite. Although depressed and discouraged, Banting tried again in the early spring of 1921; this time he received permission to use a small corner of the animal laboratory. Granted neither equipment nor money, Banting did receive the aid of a young chemist who was interested in sugar metabolism. This young man was Charles Best. With an idea, three month's time, a valuable assistant and a few disreputable dogs, Banting and Best began their work on May 16, 1921. Seale Harris (36) states that during the summer of 1921 Banting and Best achieved a reputation for stealing dogs, because of which the University of Toronto fell into such disrepute with the owners of pet animals, that at a public gathering of some kind in Convocation Hall, a woman arose and said: "Mr. President, I would like to know what the University did with my black cat!?" Although this statement was denied by Best, it is known that the inadequate laboratory, they were given by Macleod during the summer while he was away, became the best equipped by the time he returned. The two young men had been busy requisitioning without consent beakers, lab dishes and other necessary items from other laboratories.

The atmosphere in the laboratory was far from light-hearted. Their initial ligations had failed and the pancreases of the dogs had not atrophied. More then six weeks of valuable time had disappeared. Discouraged, more dogs were prepared. This time the ligation held and the pancreases were extracted. The extract injected into dogs produced a significant lowering of blood sugar. The mysterious internal secretion of the pancreas had been obtained in a utilizable form.

When J.J.R. Macleod returned in the fall of 1921 prepared to request the departure of Banting, he found that Banting and Best had isolated the substance that had baffled the great minds dealing with sugar metabolism, including his own. The entire force of Macleod's laboratories was placed at the disposal of these two young men. Numerous were the conflicts between Macleod and Banting. Banting was the backward, undistinguished, unknown, poor, untrained country bumpkin, who, according to Macleod, had accidentally discovered insulin with the help of Best. Another dispute concerned the name of the newly isolated substance (33). Banting and Best wanted to call it "Isletin" while Macleod insisted that the name "Insulin" given it by Sharpey-Shafer (35) should be retained. In this dispute, Macleod prevailed. In yet another episode, Banting steadfastly stood for the recognition he believed was his due. Macleod was trained in the European clinics at the turn of the century where the system prevailed that the head of the department or clinic was to receive the recognition for all discoveries in his laboratories whether he knew of the work or not. In fact, at the May, 1922 meeting of the Association of American Physicians, Macleod presented the paper which brought wide attention to insulin. In several speeches after that, Macleod credited himself et al with the discovery of insulin (33). Banting demanded and received proper credit for himself and Best. Even with this correction, the Nobel prize in medicine in 1923 went not to Banting and Best, but to Banting and Macleod.

With the discovery of insulin, the climax of the history of diabetes is reached for the present. The events to be related below, although representing brilliant and valuable work, are perfections added to the basic ingredient--insulin.

From a crude extract of a few degenerated pancreases, the production of insulin soon evolved into a large scale, life saving business. Once the novelty of insuling had waned and production of insulin was under control, the search for means of improving the insulin, for cutting down skin reactions, for diminishing the number of injections and for more constant control of the blood sugar began.

In 1927, Abel (37) and his collaborators reported that insulin had been crystallized. With a pure product, those who suffered reactions from the extraneous matter in commercial insulin were helped.

It was not until 1935 that Hagedorn, Jensen, Krarup and Wodstrup (38) reported the next significant advance in insulin therapy. They combined insulin with a simple protein, protamine, and found that the hypoglycemic action of insulin was prolonged. This was substantiated by various clinical workers, including Root (39) and Joslin (40).

Scott and Fisher (41,42,43) noted that zinc would prolong the action of crystalline insulin and that spermine and zinc added to insulin produced an even longer hypoglycemic action. They also noted that the addition of zinc to protamine insulin extended the hypoglycemic action of that compound. Through the work of Hagedorn and Scott and Fisher a new principle was propounded--that the addition of an insoluble substance to insulin to form a loose compound would prolong the action of insulin in the body.

This new compound was not received wholeheartedly. Hypoglycemic reactions the morning following an injection and the slow onset of action following injection were not at first understood. However, PZI soon became a valuable addition to the clinicians' armamentarium. With this principle in mind, Gray, Bischoff and Sansum (44) formed a compound of insulin and histone. This, they found, had an advantage over PZI, in that the duration of action, as shown by various clinical studies including those of Barnes (45), was slightly less then 24 hours. To have a compound that would approximate the 24 hour day in its hypoglycemic action was the object of still further research, since histone insulin was found to be less predictable in its action then PZI (46). In 1939, globin insulin was introduced by Reiner, Searle and Lang (47). Its hypoglycemic action was similar to that of histone-insulin. It reached peak action in 10-14 hours and was effective for approximately 24 hours, according to Marks (48) and Bauman (49). It was apparently stable and relatively predictable but failed to overlap enough to prevent early morning glycosuria (50).

Clinicians were not completely satisfied with the above compounds. As a result, some of them attempted to blend their own insulin, like a good tobacco. From the use of mixtures containing various proportions of PZI and regular insulin came a modified insulin--NPH. MacBryde and Roberts (46,55), Colwell and Izzo (51), Dolger (52), Peck (53) and Marble (54) were among the workers who contributed to the development of NPH insulin. This product has an activity curve which allows sufficient overlapping between daily doses to prevent early morning glycosuria and yet not cause nocturnal hypoglycemia.

The next major advance was that produced by Hallas-Møller and his group (56). They discovered that insulin alone in a precipitated amorphous or crystalline state, together with a small quantity of zinc, gives a protacted effect without employing protamine, histone or globin. By varying the particle size and the proportion of amorphous to crystalline insulin, they have been able to vary the duration of the hypoglycemic action of the insulin. The various insulins are the Lente Insulins. Semi-Lente has an action curve of approximately 30 hours, Ultra-

Lente a curve of 18 hours, while that of Lente is 24 hours and resembles the curve of NPH insulin (56).

Attempts have been made from the time insulin was discovered to find some way to give insulin orally. Murlin and Gibbs (58), and Driver and Murlin (59) in the early 1940's attempted to produce hypoglycemia by giving insulin in combination with hexyl resorcinol and various buffer mixtures. These attempts were unsuccessful in that the insulin continued to be destroyed by intestinal enzymes. Chen, Anderson and Maze (60) in 1946 reported on a sulfonamide compound which caused a fall in blood sugar in dogs when given orally. They felt that the production of endogenous insulin was stimulated by this compound. Houssay (61) found that the oral administration of two new organic compounds containing sulfur produced a) protection against the diabetogenic and toxic action of alloxan, b) decrease in frequency of occurrence of diabetes subjected to ablation of 95% of the pancreas and c) increase of free sulfhydril content of the liver and certain other tissues. Francke and Fuchs and Bertram, Bendfeldt and Otto (63) reported on a hypoglycemic producing sulfonamide preparation in 1955. Francke and Fuchs felt that this compound, called BZ 55, blocked the A-cells of the pancreas causing a preponderance of the homorganic insulin in the B-cells. This is based on the idea that there is a hyperglycemic glycogenolytic factor secreted by the A-cells of the pancreas which counteracts the insulin (64).

At the present time, the state of oral insulin or insulin-like compounds is experimental. Whether it will prove effective and worth clinical application remains to been seen. If useful, it will be another advance in the administration of insulin much as Hagedorn's idea of prolonging the action in injected insulin was an advance over regular insulin. The only advance which will parallel the discovery of insulin will be the elucidation of the etiology of diabetes. Will it take another Banting or will it be the work of a great laboratory directed toward that object? We can hope for another Banting.

Summary and Discussion:

The history of diabetes was given. To summarize a paper which is already a summary of so vast a topic would be like summarizing the sentence, "Insulin discovered." Therefore, the reader is referred not to the bibliography but to the body of the paper for his summary.

At the start of this paper, the author stated that in some ways the definition of diabetes as given by Joslin (1) would be explained. It is his feeling that this has been done, but with the exceptions noted below. Hyperglycemia was noted by Doseux (10) and Dobson (6,7,8). Glycosuria was known to the ancient Hindus (7) and described for the western civiliztions by Willis (12). That there is either a deficient formation or diminished effectiveness of insulin was shown by Banting (5,33) by administering an additional amount of insulin to diabetic patients and noting the hypoglycemic response. That the islets of Langerhans were responsible for secreting the hypoglycemic factor was shown by von Mering and Minkowski (25). The histology of the islets of Langerhans was not discussed and the reader is referred to Homans who in 1915 showed that the B-cells secreted insulin (8) and the work of Goldner and Gomori (64) on alloxan diabetes. That diabetes was interrelated with conditions arising in the liver was early shown by Bernard (15,16). The relationship of pancreatic diabetes with other endocrine glands and with hyperglycemic factors was not discussed. However, the reader is referred to the work of Houssay (66), to Price, Cori and Colowick (67), to Pincus and Gutman (68) and to the excellent bibliographies of these authors.

To write a complete history of diabetes would be no less then a life long research task. In spite of his briefness, the author hopes that this paper will in some way shed a small bit of light on the so-called "dry" field of history. He attempted to tell a story, roughly following the evolution of the understanding of diabetes. In telling this story, he at times used levity, at times expressed his own opinion, and at times merely stated fact after fact. These changes-of-pace were used to bring life to history. We should all remember that today we are living in the history of one day hence. We do not consider our living uninspired and without animation; therefore, why should we yawn and be bored when we seen the word history in a title? History lives, just as we live. Without the history in our own personal lives, we would be naive and out of place in our dealings with the rest of the human race. So it is with disease. Our attitudes towards a particular disease would be naive if it were not for the experiences recorded in history.

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