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History of diabetes

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by

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The true origin of diabetes must necessarily remain a well guarded secret of nature, since there are no visible or tangible remains of the disease in the preserved portions of early man. Unlike tuberculosis, syphilis, or arthritis the evidences of which are visible in the osseous remains found by the archaeologists and dated prehistorically by them, or like smallpox, the lesions of which have been found on the skin of Egyptian mummies, diabetic history is confined to the period of the written word. (54), (53), (21), (8). When the first gene skipped from chromosome to chromosome making the tendency to diabetes a recessive character in the human germ plasm, we will never know. Or, perhaps it has allways been there. But, whether or not it has allways been present in the constitution of the human race, or whether it is a relatively recent acquisition, the fact remains that at the present time diabetes is one of the major health problems of the present day. It is taking its increasing toll from all types and classes indiscriminately.

The last two and a half decades constitute perhaps the most interesting period in the history of the disease for within that period fell the epoch-making discovery of insulin treatment for the diabetics. Such a development would have been of the highest interest in connection with any disease; but it has a particular significance because it is the only instance so far in medicine of an efficatious specific treatment for one of the major chronic diseases characteristic of later life. The discovery of insulin in 1922 by Banting assisted by Collip, a biochemist, and its later commercialization

to the public at a nominal figure, have materially improved the prospect of the diabetic. Yet, surprising as it may seem despite the materially improved prognosis of the disease, its death rate is not decreasing. In fact it has been on the increase. The answer to this paradoxical question is the fact that lends interest to the latest chapter in the story of diabetes.

In 1911 diabetes, as guaged by the standardization of annual death rates at ages 1 - 74 years and discounting deaths from violence, accounted for only 1.1% of the deaths and was sixteenth in the rank of causes of death. In contrast to this in the year 1935 this disease accounted for 3.0% of the deaths and was eighth in rank. Thus, while other diseases such as tuberculosis in all forms, typhoid fever, lobar pneumonia, and acute nephritis have exhibited a marked drop in mortality rates, diabetes has advanced rapidly in the registers of mortality and may be considered as one of the outstanding health problems of the present day.(51)

There are many facts and factors which are of interest in the study of the status of diabetes as a cause of death and as a public health problem at the present time. Diabetes is primarily a disease of later life for the rate of increase varies considerably with age, in fact, from about five per hundred thousand at the age of five years to over three hundred at the age of seventy years. It is also shown that women are the chief victims of the disease. Another class which is markedly susceptible to the disease are the Hebrews. Negroes were formerly believed to be relatively immune to diabetes but time and improved diagnostic tecknique combined with free health serveces to the underprivilaged has proved this un-

true. For with exposure to conditions of urban life and having been sought out by the home missions groups these people have been found to be as susceptible to the disease as the white race.

In the young of all the susceptible classes, however, there has been a steady decline in the death rate and is of especial significance because it is due in a large measure to the use of insulin; prior to the discovery of insulin the death rate of individuals under twenty-five years of age was moderately upward. This decline also includes individuals in early adult life. Among persons past forty-five years, however, there has been a distinct rise in death rate without exception as to race or sex. This rise has been most marked among women especially of the Negro race. In white males of the age group forty-five to seventy-four the death rate varied little prior to the discovery of insulin, but since insulin it has been rising steadily at the rate of 1.9% per year.

The present trend of diabetes mortality in to seek a level. But this level is at a far higher plane than that which prevailed at, say, twenty years ago. In the relatively short span of ten years (1924-1934) the rate increases 25%. Yet even this advance is but the continuation of a broader rise in the death rate from this cause which began in the first decade of the twentieth century and which has only been interupted at three points, <u>vis</u>, (1) in the late war years and immediately following the war when it may have been influenced by the restrictions on the use of foodstuffs through government regulation and high prices; (2) in the years immediately following the introduction of insulin treatment; and (3) in the present period of stability.

In summary to these facts then, we may say that the large increase in the diabetes death rate in the past twenty-five years has taken place in the face of two important advances in the treatment of the disease, namely, undernutrition, introduced by J. F. Allen in 1914, although it was an accepted mode of treatment with Guelpa of Paris in 1896 and was suggested by Bouchardat fifty years prior to that, and insulin the general use of which began in 1922, a year after its isolation by doctors Banting and Best. (5),(20),(7). The benefits of these innovations in diabetic treatment to the diabetic patient have been marked and unmistakable. It must be realized, therefore, that the increase in the death rate from the disease has occurred in spite of important improved treatment. The causes of this rise in the recorded rate are to be found, first, in an actual increase in the crude and the standardized mortality due to the great changes that have taken place in the modern social milieu and, second, in an apparent increase arising out of the advanced medical science and in the growth of medical facilities which have resulted in the more frequent diagnosis of the disease.

What specifically may we find to be the cogs of the social machine which are moving to make these facts true. First of all we have the population changes. This is probably the most important factor of all in the increase of the crude death rate. These changes have resulted in a marked increase in certain groups in which the disease most commonly occurs. Chief among these is the rapidly growing proportion of older people due in greatest measue to the decreasing birth rate and to the decline in the mortality during the first half of life. Another feature of change in population which has

a bearing on the subject has been the shift from country to city. In the relatively short span of about thirty years we have become an urban population. And, as may be pointed out, diabetes takes its largest toll among the city dwellers. There has been too, a rapid growth in those foreign race stocks which are particularly susceptible to the disease, notably, the Hebrews whose high mortality from diabetes is well known. As a result of these developments, the population susceptible to diabetes has been growing rapidly.(44)

This changing population, moreover, has been subject to two great social forces which have a direct bearing on the incidence of diabetes. The first of these is the rapid extension in the use of machines driven by mechanical power in every line of human endeavor,- in the field, in the factory, in the office, and in the home. The result has been to make man more and more a tender of machines, and to reduce enormously the expenditure of his own energy in his work. Moreover, it is significant that the greatest use of machines is in the factories located in the urban centers which constitute the fastest growing part of our population. However, this mechanization has not been limited strictly to the cities and towns, for more and more machines have been introduced to the rural population and these areas have come to take on, in quite some measure, the aspect of the more populated centers. The other great social force which is more or less a corollary of the first, has been the long time rise in the standard of living of our population. This is a result of and increase in real wage, which, during the most of the last three decades, progressed at a rate unprecedented in the history of our own, or any other country.

Consequently as a people we have been able to command both the necessities and luxuries in an abundance as never before. This change is significant in that it has favored an over-indulgence in food and drink, if not absolutely, at least relatively in proportion to the energy requirements of large numbers of people. These outstanding forces bear directly on the diabetes problem because the disease takes its greatest toll among the overweight persons. Analysis of insurance stastistics shows that the subsequent diabetes death rate among healthy over weight men who were able to pass Life Insurance examination and to take out insurance to be two and one-half time that of average weight men and four times that of under weight men.

As has been mentioned before, the improved diagnostic technique made possible to the medical profession in relatively recent times has been a factor of no mean proportion in the increase of diabetes mortality in the statistician's figures. For the definite diagnosis of diabetes in the early stages of the disease is based of the findings in the biochemical laboratory. As a whole this laboratory technique is relatively modern, and the methods which make possible a diagnosis that is both quick and sure are relatively new. The essential elements in the making of an early diagnosis are the blood sugar lever and the established presence of sugar in the urine.

The method most often used in this country for the determination of blood sugar level from a small sample was first evolved by Folin and has been in general use sunce 1928. The methods in use before that time were more complicated and envolved thus causing a predisposition to omit this essential

measure. The methods for the determination of sugar in the urine are much older dating back, in fact, at least to ancient Hindu medicine where the name given the disease signified " Honey Urine ". However, the quantitative method we use now was discovered in 1909. The laboratory diagnosis of diabetes used to be made on the basis of urine findings only, but methods of ruling out glucosuria that was merely transient by the giving of measured amounts of glucose came into general use only about 1920.

On account of the ease with which these preceedures may be carried out their use has expanded enormously; thus in the medical examination of the sick, analysis of the urine for sugar and in suspicious cases of the blood has become a routine proceedure. The advancement of this practice has been favored by the increase in the number of laboratories in the new and old hospitals and in the offices of practitioners. Moreover, as the years have passed a new generation of physicians has come which has been trained in these newer teckniques and is imbued with their value and use. On the other hand the pendulum may have swung too far in the other direction and often it seems as though the clinical story of the patient were lost in an amassed array of laboratory data of acedemic interest only. This is particularly true of our teaching institutions much to the befuddlement of the student who is taught to put too much dependance on laboratory work that will not be available to him when he is out in practice.

Thus we see that, not only has that portion of our population which is most susceptible to diabetes increased greatly,- namely, older people, particularly women, city

wellers, and certain foreign race stocks - and the conditions of life changed in such a manner as to favor the development of the disease, but the probability of its being detected is also increased, especially in the earlies stages of the disease. It is not surprising, therefore, that the number of persons known to be suffering from the disease has grown apace and that the number of deaths charged to the disease has likewise grown.

The epoch making discovery of insulin during this same period farther complicated the picture. After the discovery of insulin the opinion prevailed generally that following its use on a wide scale the death rate would decline continously. This view can only be based on the mistaken idea that insulin cures deabetes. It is, however, simply a specific means of treatment, wonderfully effective and valuable, for a disease which is not yet curable by any known means, but which can be controlled in such an excellent manner by present methods of treatment, of which insulin is only one aspect, that, in most cases the patient can lead a nearly normal life.

Thus, while insulin has been an enormous benefit to diabetics, it could not in its role as a specific means of treatment, and not a cure, be expected to check the rise in iabetes mortality which is primarily due to the increasing incidence of the disease. The truth of this observation is proved by stastistical evidence which shows the improvements in the diabetic situation brought about by insulin.

The most striking proof of the value of insulin is its success in prolonging the life of diabetic children. As we have seen diabetes is disease of later life primarily

and is relatively uncommon in children. When the disease does occur at younger ages, however, It is most severe. prior to the discovery of insulin, the disease in children terminated fatally within a short time. (27) The hopeless situation of the diabetic child of that time was most graphically described by Dr. Joslin vis, " The parents of diabetic children were panic stricken and the doctor broken hearted when they learned the child had diabetes. One of the most noted children's specialists in the United States wished that he might never have to see another diabetic child so sad was it to see the child starve to death. The average life of the diabetic children was surely less than a year and that of the largest group of diabetic children in the world under careful observation was under two years. Undernutrition was the only means of prolonging life, and was permitted by the despairing parents simply for hope set before them that someone would discover something which would save their child. Now the death rate among children has fallen to small fraction of what it was formerly.(25)

Another impressive proof of the value of insulin is the decline in the deaths from diabetic coma. Formerly these deaths predominated but are now the exception, even in childhood where formerly deaths from come were most dreaded. The improvement in this aspect of diabetes is most clearly illustrated by the experience of Joslin twenty-five years ago, one out every two deaths among patients was due to coma. but in the past five years the proportion of such deaths has fallen to one in sixteen. Thus, in contrast to the increase in the death rate from diabetes, the death rate of diabetes has definitely improved.

The consideration of these aforementioned factors affecting the trend of diabetes mortality rates leads to the conclusion that the crude death rate from the disease may be expected to continue upward for some time; probably until a period of population stabilization is reached. This view should not be considered a pessimistic one. Altogether the outlook is favorable. If, despite these facts a source of alarm is seen in the rising death rate from diabetes reassurance may be gained from the presence in this country of many hundreds of happy, active diabetic children, leading normal lives through the aid of insulin, whereas hardly more than a decade ago the diabetic child was doomed to death after a few months of miserable existence.

In view of the place which diabetes has gained in the annals of diseases and because of the fact that even if the present level of mortality does not rise, more than 2% of the population will eventually acquire the disease, diabetes has been made an important problem in the field of preventative medicine. To a far greater extent than cancer of heart disease, diabetes is amenable to certain definite methods of control by using the present knowledge of the development of the disease, and its treatment, and its complications. The problem is two fold. The first and most important is prevention of the disease. The other aspect is prolonging the life of the diabletic patient. The prevention of the disease is largely a matter of education in matters of: detection of likely candidates for the disease, eugenics, and, the contributory factors likely to precipitate the disease. (44) If we paid as much attention to the condition of our own stock as we do to the breeding of our animals, diabetes and

all such like conditions would soon be diseases of the past. This is as yet, however, an affront to civilization and therefore impossible.

Increased longevity and comfort for diabetics will evolve from the action of such forces as: improved treatment with and the use of insulin through farther research, prevention of coma, diet, controlled excercise, periodic checkups, free clinics, and such organizations as the V. N. A.

These programs of prevention and organization of medical facilities will bring diabetes under some measure of control. The number of new cases may be reduced to a minimum by bringing the attention of the public to the role that heredity and obesity play in the development of the disease. On the other hand the life of the diabetic may be prolonged by a well rounded program to combat the disease. This program in which physicians, public health workers, and patients can co-operate, will yield worth while results in securing early diagnosis for the diabetic and in keeping him a useful and healthy citizen quite unlike that hopeless invalid - the diabetic of little more than two decades ago. (15),(44)

With this picture of the diabetes of today before us, this picture which in all probability will be antiquated in another few decades by the discovery of the cause and cure for the disease, let us turn back to our knowledge of the earliest beginnings of the disease. That it is a disease of great antiquity there is no doubt, but as has allready been mentioned we must necessarily confine its history to descriptions and explanation found in ancient writtings. Many times these do not give a name to the condition described and the name must be supplied by us in the light of our pre-

sent knowledge. We must fill in for our less endowed predecessors, and yet, are we so far superior to them in the healing art? True, we are scientists, exact in every detail, and knowing of all diagnoses. But also true, is the fact that our hospitals are full and Death is as yet several jumps ahead of us. We may be a little, but not much, closer to the final goal of universal health and happiness for all than were the priests in the ancient temples of Aesculapius.

Egypt: The Papyrus Ebers, while it is the longest and most famed of the Egyptian papyri which deal with subjects magical and medical, is not a book in the true sense of the word but a miscellaneous collection of extracts and jottings from at least forty different sources. It consists mainly of a large collection of prescriptions for a number of named ailments, specifying the names of drugs, the quantities of each, and the method of administration. A few sections, however deal with diagnosis and symptoms, and here we find mention of an abnormal polyuria which is now believed to be diabetes. (8)

Early Greek: Hippocrates studied human disease from an objective standpoint, recording case histories and observing the patients symptoms as none has ever done before. It seems, however, that he did not distinguish diabetes for in his writings there is no clearly defined description of this (6) disease. In the light of his thoroughness and insight of human ailments may we then assume that there was no diabetes at this time? This hardly seems likely, for there is a much more reasonable for the omission. Hippocrates lived during the reign of the Pythagorean philosophy. This line of reasoning stated, or had for its precepts, that no attempt should

be made to cure a thoroughly incurable diseased system and so afford a long and miserable life to the man himself as well as his decendants. For Aesculapius did not think a man ought to be cured who could not live in the ordinary course as, in this case he would be of no use to himself or to the state.(35) It is understandable why Hippocrates, living in such and atmosphere refrained from treating an incurable disease and probably why he neglected to mention diabetes, which to his analytical mind would have cut a clear picture hardly to have been overlooked.

Greece: Aretaeus, the Cappodocian, however, living a few years later(30-90 A.D.)did not accept the Spartan Doctrine of the Pythagorean Philosophy, but he believed that all life should be prolonged by the use of medicine whenever possible and that the physician should attend an incurable patient even if he had only sympathy to offer. (35) This attitude coming about 50A.D. was perhaps directly due to the coming of Christianity with its doctrine of love and the brotherhood of man. Aretaeus gave a good description of diabetes in which he remarks that diabetes is a wonderful disease, being a melting down of the flesh into urine. The disease, he says is of slow formationbut when fully formed is speedily fatal. His descriptionof the symptoms are striking, In fact it was he who coined the word dia-betes, which means "to pass through". He called attentionto the fact that the disease is often associated with acute infectious diseases but did not mention the presence of sugar in the urine. (1)

Rome: Aulus Cornelius Celsus (30 B.C.-50 A.D.) while not a practicing physician was never the less a very learned and versitile gentleman. He wrote treatises on medicine as well

as on agriculture and other subjects. Greek medicine reached Rome before the Christian era and Celsus, a Roman, translated the Greek medicine of his day, writing an admirable summary of the medicine and surgery of the Hippocratic and Alexandrean periods.(42) He left a good descriptionof diabetes which was the one Aretaeus in a large measure adopted, claiming, however that patients afflicted have a discharge of urine greater than the amount of fluid taken in by mouth. While this statement might be the subject of controversy now, it appears to have been taken for its face value for 1800 years.(6)

India, China, and Japan: Hindu medical writings of the sixth century refered to the disease as Madhumeha, or "honey urine". (19) From the Susruta, one of the three leading texts of Brahminical medicine, (fifth century A.D.) we find that diabetes is a disease of the rich and one that is brought about by the overindulgence in rice, flour, and sugar. The order of the disease is ushered in by the appearances of morbid secretions about the teeth, ears, nose, and eyes. The hands and feet are very hot and burning and the surface of the skin is shiny as if oil had been applied to it. This is accompanied by thirst and a sweet taste in the mouth. The different varieties of the disease are distinguished from each other by the symptoms of deranged humors and the color of the urine. If the disease is produced by phlegm insects approach the urine; the person is languid; he becomes fat, and there is discharge of mucous from the nose and throat with dyspeptic symptoms and looseness of the skin. He is allways sleepy, with cough and difficult breathing.

1. In this disease the urine is nearly of the natural color without any sediment.

2. The urine is like the juice of the sugar cane in color and taste.

3. In this variety the urine becomes thick after standing some time.

4. The urine is of white color, it is thin and pure above and thick below.

5. At the time of micturation, the hair over the body is erect and the urine has a copious white powder as if flour had been mixed with it.

6. In this variety the urine is the color of semen which sometimes appears mixed with it. In the chronic form this is incurable.

7. When the urine lets fall a hard and small deposit like sand.

8. When there is a copious secretion of urine which is sweetish and cold.

9. When there are frequent calls to make urine which is discharged in small amounts.

10. When the urine is like mucilage and has long strings of adhesive matter mixed with it; it is cured by means of astringent decoctions. (55)

This is the diabetes mellitus which was known to the Hindus and its dangers fully appreciated before it was known in Europe. All the hereditory and congenital forms of the disease are incurable; and if not properly treated will terminate in sweet urine which is incurable. (6)

From the conditions of the urine described and the conclusion drawn that if proper treatment is not ordered, the fatal sweet urine will appear, it would seem that infectious processes present were interpreted as prodromal symptoms

of the disease. And these, in patients with a tendency toward diabetes would rapidly precipitate the disease and bring about death. This would indeed complicate the classification of the disease.

Among the Chinese and Japanese, while their oldest epitome of medicine was compiled about 2637 B.C., the first attempt at scientific medicine, if it may be dignified by that name, is recorded about 229A.D. by Chang-ke. At that time they wrote that the urine of diabetes was very large in amount and was so sweet that it attracted dogs, and in the description of the disease they noted the furunculosis.(55)

Arabia: Razes (860-932) an Arabian physician lived during the golden age of Arabian medicine. Unto him came the honor of directorship of the hospital of Bagdad. He developed into the chief clinician of the Arabian school, his material being so extensive that in recommending a treatment for sciatica, he was able to say that he had seen this method tried successfully on a thousand patients.(42) He made brief comment on diabetes. (6)

Avicenna (960-1027) prince of the physicians was the great Arabian physician of his day. He was immenently successful as a court attendant and Vizier to several Caliphs. He died in the prime of life from drinking too deeply of its pleasures and vices. Let it be said to his great credit, however, that he worked as hard as he played. He is said to have written over a hundred different articles on different subjects and his Canon was an attempt to codify the whole of the medical knowledge, much as we do the modern systems or encyclopoedias of the present time. He was undoubtedly a great clinical genius and a great medical writter.

He observed that diabetes may be primary or secondary to another disease. In this he follows the teaching of Aretaeus. He observed that diabetic patients have a great thirst, nervous exhaustion, an inability to work and a loss of sex function. He believed that in diabetes the liver was affected, probably because he saw some cases of bronze diabetes with enlarged livers. He observed that carbuncles and phthsis are frequent complications. He described diabetic gangrene and, finally, it was his opinion that no treatment was effective. One may well ask what are the clinical features of the disease, as we know it today that Avicenna did not describe. He did not, however, mention the sweetness of the urine.(12)

Unburdened by tradition, fresh from nature observation, ancient Greece erected the structure of scientific medicine. Much of this structure stands today, but with the passing of time Western culture became sterile of any new thought or ideas and to the Arabians was thrown the torch of the medical knowledge handed down from the Greeks. They faithfully held the light but added no feul to the flame, and, as time passed, a new foundation was needed - the foundation of anatomy and physiology. Medievalism could not build this foundation , because the materials were lacking. The alleged differences between the three great Semetic religons stained continents with blood but shrank with equal horror from the anatomists knife. All united in the belief that whoever touches a cadaver is guilty of sin, and medicine remained without a true basis for centuries. Hence Arabian medicine could not endure and under accumulating knowledge it collapsed completely. Had the Koran not forbidden dissection, the gifted Arabians would not have been mere copyists of the Greeks. Had Rhazes, the

most gifted member of the Arabian school, been permitted to explore the human body he would not have said,"If Galen and Aristotle are of one mind on a subject, then of course their opinion is the right one. When they differ, however, it is extremely difficult to know the truth." This is the tragedy of Arabian medicine.(42)

While the Arabians were raiding the West for authentic Greek amnuscripts and the Europeans were raiding the far East for religious relics and Europe was in the gloom of the Dark Ages, medicine made no progress. With the passing of Galen at the end of the second century the thread of rational medicine snapped and the science of antiquity had run its course. Medicine then spun a ghostly loom and a strange mysticismcame over men bringing with it an adoration of odd numbers and dirt and dung from wagon ruts to cure the colic. Classics which should have been immortal perished, while the rubbish of Serenus Sammonicus, the author of the ABRACADABRA survived, for its formulas were repeated in countless incantations, and the sick wore the magic word. We have no new word of diabetes during all the Middle Ages. (42)

The next mention of diabetes came after the dawn of the Renaissance when European medicine cast off its shroud and reawoke. Sylvanus, or Jacobus Sylvius, (1478-1555) was the first to reopen the question. He was a staunch exponent of Galen and went so far in his defence as to be absurd. For instance, when Galen had said that our thigh bo nes are curved, and a cursory glance revealed that our thigh bones are straight, Servius still asserted that they are curved in a state of nature, and that their straightness was due to the narrow trousers which men wore. (42) Sylvius believed that

diabetes was a disease of the blood, and although there is no mention of it, it would be a safe surmissal that this was also the opinion of Galen. (7)

Aureolus Phillipus Theophrastus Paracelsus Bombastus von Hohenheim (1493-1541) was the great censor of all times. While acting as Professor at the University of Basel, one day in the presence of his class, he placed some sulphur in a brazier, set fire to it and cast in the sacred volumes of Galen, Avicenna, Averroes and other medical masters."Follow me",he cried, "not I you, follow me!" He denied the four humors of the old pathology which dated back to Hippocrates of Cos. He asserted bombastically that these humaors did not exist and he tried, and successfully often, to discredit many of the medical ideas of his day. He was learned in chemistry and evaporated a liter of diabetic urine and recovered four ounces of "salt" which he said made the kidney thirsty and caused the polyuria.(48)

Cardano, another doubter, (1505-1576) not accepting the dictum of greater outout than fluid intake, compiled a table in which he recorded the liquid intake and theuninary output of his diabetic patients. (6)

Thomas Willis (1621-1675) the leading exponent of chemistry was noted for his close clinical observations. He claimed that diabetes was primarily a disease of the blood and that the sugar first appeared in the blood and then later in the urine. He made the best qualitative examination of the blood possible at the time and noted its sweetish taste. He thus established the basic principle for the diagnosis between diabetes mellitus and the insipid form although he was not the first to note the sweetness of the urine.(19)

Brunner (1682) discovered that removal of the pancreas in dogs produces a polydipsia and poly uria in the animals. But he apparently did not realize the significance of his findings or know that the organ had a digestive function. The interpretation of his results had to wait for nearly two-hundred years more to pass. How much ahead of ourselves would we be in our handing of diabetes had Brunner established the pancreas as the etiologic organ of the disease at that time.(32)

For the next century attention focused on the urine of diabetics and its examination. Robert Wyatt in 1774 claimed the presence of a sugar like substance in the blood and in the urine and recovered it from the urine by evaporation. Dobson, (1776) claimed that the sugar present is one that ferments. Johann Peter (1745-1821) defined diabetes insipidus as diabetes without glucosuria. Crawley in 1788 for the first time diagnosed diabetes by demonstration of sugar in the urine. He also observed that diabetes may result from injury to the pancreas such as occurred in a case in which at post mortem he found a pancreatic calculus. (7)

Rollo in 1796, an Englishman, should be credited with having laid the foundation for treatment by restricting the diet. This was the beginning of the period of Empiric Treatment. He also described a patient twenty-five years old with the odor of decaying apples on his breath and denied the out-put greater than intake controversy.(13)

More work was done on the urine. Latham, in 1811, farther differentiated diabetes mellitus from diabetes isipidus. Cheveul(1815) identified the sugar as grape sugar, and Eberle in 1831 observed that,"The diabetic urine enters very slowly into the putrifactive decomposition, but passes readily

into acetous or vinous fermentation. (19)

Then came Bouchardat (1806-1886) with whom the modern view point of diabetes begins. We may really say that in the last sixty years more has been accomplished in the study of diabetes than in all the preceeding 1850 years. His work was truly remarkable. He used the fermentation test, the polaroscope and copper solutions for the detection of sugar. In the treatment of diabetes he urged the use of fresh fats as a substitute for carbohydrates, the avoidance of milk because of lactose, and the use of alcohol as food. He invented gluten bread, stressed the advantages of using green vegetables, insitiuted fast days, and stressed the advantages of undernutrition. He prescribed excercise for the diabetic and administration of alkalies. He called attention to the fact that during the seige of Paris, when food was scarce, glucosuria disappeared in diabetic parients, just as it did in Germany eighty years later during the World War.(6)

From the time of Avicenna to Bouchardat is some eight hundred years. The former gave us the best description of the disease to his day, and the latter laid down the most rational treatment up to his day. Both were empiric, but they marked great strides over preceeding periods.

The necessary steps for progress to continue in this work is the study of metabolism. But, before entering upon a discussion of metabolism and its relation to diabetes, let us recall the names of a few of those who paved the way: Galen, Servitus, Columbo, Cesalpinus, Sarpi, and best known of all, Harvey, the great crystalizer of all knowledge pertaining to (if not actually the real discoverer of)the circulation of the blood . Hemmeter credits the lesser circulation to Servitus

in 1546 and the discovery of the greater to Cesalpinus in 1569. Harvey's description came in 1628, and although Harvey is generally comceded by the English speaking world to be the discoverer of the circulation of the blood, it is said that he was sorely perplexed because he could not understand the purposes of the blood's rapid flow throughout the body. (22)

Two hundred years elapsed between the time of Harvey and that of priestly and Lavoisier. Priestly discovered oxygen and Lavoisier made the first "Basal Metabolism" estimation. He discovered that the "B.M.R." is incresed by food, work, and cold.(18) When we realise that the knowledge of metabolism is the first essential in the study and true understanding of diabetes, the importance of the place which Lavoisier holds in the history of the disease is clearly defined. One is saddened at the thought of how little the world about him appreciated him. Says Lusk, "To the darkness of the History of the time (the days of the French Revolution) belongs the fact that Lavoisier, begging for only two more weeks of life, in order to complete some experiments was denied these fourteen days and was guillotined, thereby becoming one of the greatest sacrifices to the insensate fury of his age."(31)

Lavoisier (1743-1804) proved that oxygen and not nitrogen is essential for respiration and that animal respiration is a process of oxidation. He showed that when plants burned, CO-2 and H2O were the resulting products."Animal and man, like a burning piece of wood absorbes oxygen and eliminates carbon dioxide." Lavoisier actually laid down the foudation for present day physiologic chemistry to rest upon. (18)

The early work of Pettenkofer and Voit, Lehman, Ebstein,

Leo, Magnus-Levy, Kaufman, Van Noorden and many others sll indicate that the caloric need of the diabetic is equal to that of a normal man. And, if there is any abnormal deviation at all it is on the side of greater than normal basal metabolism. Ordinarily oxygen consumption, carbon dioxide elimination, and heat production are normal or above normal in the diabetic. (18)

Hirschfeld in 1895 showed that the absence of carbohydrate from the metabolism is the causative factor in acidosis.

Petter in 1875 discovered acetone in diabetic urine.

Kaulick distilled seven hundred pounds of diabetic urine and purified enough acetone to identify it by elementary analysis.

Kussmaul noted acetonuria in 1874.

Stadelman in 1833, a pupil of Naunyn, discovered b-oxybutyric acid and recognized that diabetic coma was the resuly of the accumulation of excess acids.

Minowski elaborated and confirmed Stadelman's work.

Kraus, Naunyn, Magnus-Levy, Levine, Saundly, Williamson, Von Mehring, Van Noorden, and many others have studied the disturbed metabolism of diabetes and given us most of the knowledge we now posses. In fact, it is interesting to note that some unsettled questions in the early days are still unsettled question today.(6)

While the work on metabolism was covering great strides, men studying diabetes along other lines were adding other plaques which will eventually fill out the whole mosaic. Von Stosch in 1828 propounded the neurogenic theory of diabetes, claiming that the disease was of cerebral origin. (6) While this is a more elaborate theory, it is not much more practical

than, if as near the truth actually, as Paracelsus' theory of a salty thirsty kidney.

Addison and Sir William Gull (1851) described xan thoma diabeticum. Herman von Fehling developed the well known test for sugar in 1848. Brucke and Bence Jones (1875) demonstrated the presence of small amounts of sugar in the urine of normal persons. This was verified by Pavy and described by him in the Croonian Lectures in 1878. (18)

At the same time, Claude Bernard, famous and idolized in the minds of all physiologists for his many original experiments, demonstrated sugar in the blood taken from the right heart. He produced much confusion asto the etiology of the disease when he produced glucosuria by puncturing the floor of the fourth ventricle causing "pique diabetes". The reason for this is as yet not entirely satisfactorily explained. He showed that in diabetes there is primarily an excess sugar in the blood and after that in the urine. In this he was anticipated by Wyatt and Dobson. He was the first to study the glycogenic function of the liver and after isolating glycogen he said," It is the internal secretion of the liver". As early as 1856 he made important studies of the pancreatic juice pertaining to the emulsification of fats, their passage through th intestines, and power of converting starch to sugar. But, like Brunner, he passed this gland over at this point delaying our history again. Again and again we are brought up to the cliamax as we now know it to be and are left literally sitting on the edges of our chairs in anticipation only to have the screen go blank. The Gods of medicine as well as those of lesser Arts grind slowly. Even at this time,Bernard, the industrious, was doing accurate

blood sugar determinations on some of his patients.(17)

Pavy (1829-1911) devoted twenty years to hard work on this disease. After making simultaneous blood and urinary sugar determinations, he came to the conclusion that there is a definite relationship between the degree of hyperglycemia and glucosuria. This was later verified by Van Noorden. Pavy believed that sugar was not made and was usually not stored in the liver. Pavy insisted that by dietaty management alone the urine will become sugar free and health restored, even if at a future date the glucosuria might return. Diabetes, he said, is a progressive disease, the underlying pathologic conditions making gradual advancement. He compared the course of the disease to that of locomotor ataxia in so much as there are quiet periods alternating with periods of progress, and believed by strict dieting the life of the patient would ultimately be prolonged. (39),(40)

Trousseau was the first to distinguish bronze diabetes. His description reads:" There was almost a bronzed appearance of the countenance and blackish color of the penis. Autopsy showed a cirrhotic liver of almost two times normal size.(49)

Van Noorden believed that both the thyroid and the liver played an important part. He made observations on the metabolism in the disease, anticipating many present day workers on metabolism in the disease. (47),(56)

Naunyn devoted almost his whole life to a study of metabolism in diabetes, diseases of the liver and of the pancreas. He is the first to employ the term acidosis to disignate abnormal collection of acids in the body. Although formation of acids goes on in normal health as a physiologic process, certain metabolic disturbances produce abnormal acids such

as uric, oxalic, and oxybutyric which oxidize to diacetic acid from which acetone is formed. Naunyn says, "By diacetic acidosis I mean the formation of b-oxybutyric acid in the process of metabolism. Acetonuria and diaceturia are part of acidosis for both substances originate from oxybutyric".

Naunyn believed that regardless of the pathologic conditions or metabolic changes in the individual patient , hereditary tendency in the diseas, the diabetic anlage, is a most important factor and dimonstrable in 30% of his cases. He accounted for three forms of the disease: diabetes of the young, of the aged, and organic diabetes, this including those groups associated with disease of the pancreas, liver, thyroid, and disease of the nervous system. "Diseases of the pancreas,"he says,"have only in rare instances been determined with certainty the cause of diabetes. These afflictions pancreatic calculi, cirrhosis, neoplasms, and cysts".(36)

After Naunyn opened the forum on the problem of acidosis, as is usually the case, his fellow contemporaries proceeded to put his ideas to the acid test. In contradistinction to Naunys's idea of the formation of acetone and diacetic acid from oxybutyric acid, Shaffer says," The first formed of the acetone bodies is probably acetoacetic acid, which if it accumulates in the body, is in part decomposed into acetone carbon dioxide, and in part reduced to hydroxy butyric acid". (45)

Says Magnus-Levy," Acetone bodies are always eliminated when carbohydrates are lacking in the organism of when they they are not used in the normal way. Under these conditions, indeed, the oxidation of protiens and fats will deficient and oxybutyric acid will appear in the urine. Acidosis does,

not only, and I repeat it again and again, or perhaps not at all depend of the formation of acids, but also, and perhaps exclusively upon their combustion".(33)

Sugar is the most combustable product consummed in the organism. When sugar is not burned total combustion is lessened and those other products which should by oxidized simultaneously accumulate unburned. Thus says Rosenfeld,"Fats burn in the flame of carbohydrates", and it still echoes in the lecture rooms. Van Noorden considers acetone a by product of protien metabolism.(37)

The greater part of the acetone bodies, however, have fatty acids as thier immediate precursors. Carbohydrate combustion is the primary oxidation, and protien and fat combustion is the secondary combustion. Magnue-Levy does not agree with this but thinks that total oxidation is a single process.(33)

Beginning with Priestly and Lavoisier who laid the foundation for the study of metabolism and the work of Petter who discovered acetone, and Stadelman who discovered b-oxybutyric acid, Nauyn, Magnus-Levy and Van Noorden whose laboratory and clinical research firmly established most of our present day ideas, we have at last arrived at a satisfactory working knowledge of the disease. (6)

As biochemical disturbances came to be understood more and more, treatment of the disease was gradually established on a firmer basis. Discovery of acidosis brought forth alkali therapy. While today we view this as a mixed blessing, it no doubt was a necessary step in the evolution of a more complete understanding of the disease. (6)

Fats and fatty acids associated with improper oxidation

led to the restriction of these substances in the diet. Protiens, another source of keytosis were also restricted, and the necessity for carbohydrate restriction was long known.(6)

Noone perhaps has stated as clearly as Naunyn, writing three decades ago, the principles which are today applicable in the treatment of diabetes. He advocates, first of all, prophylactic treatment, particularly dietetic, in those who have an hereditary tendency and further advocates the following:

1. The alpha and omega in the care of diabetics is dietetic treatment, not drugs.

2. It must be known that diabetic glucosuria increases with time while the toerance of the patient decreases.

3. When the diabetic is free from sugar his tolerance increases. Therefore, the aim is to render the patient sugar free and to keep him aglycosuric.

4. Limitation of the entire diet with resulting disencumbrance of the entire metabolism brings about a favorable result.

5. Reduction of carbohydrates and protiens for removal of glycosuria.

6. Sugar producing foods are carbohydrates and protiens.

7. We should determine the exact quantitative and qualitative diet for each diabetic patient coming under our care.

8. Patients get along well on thirty to thirty-five calories per kilogram of body weight.

9. Sugar production from fat does not play such an important part as to influence the diabetic glucosuria to any extent.

10. For this reason, and because of its high caloric value

fat is themost valuable food substance for the diabetic.(36)

How much more, may we ask ourselves, is the student taught, or how much more does the physician abreast of the times know, which carries them beyond this decalouge of diabetic science? At this time let us pay tribute to the names of Avicenna, Bouchardat, and Naunyn as great teachers. Their descriptions of the disease and treatments they recommended stand out boldly in the history of the disease.

Van Noorden in 1895 advocated the oatmeal diet. The benefits obtained were mainly due to the fact that the total caloric value and the protien content of the diet were lowered. (6)

Guelpa in Paris in 1896, began the treatment of diabetes with periodical fast days, although Bouchardat had thus advised fifty years prior to this time. Guelpa advanced this as a method of detoxicating the patient. He demonstrated that by fasting and saline laxatives the patient is made sugar free in usually three days. (20) He finally convinced the most skeptical ones around him but his contemporaries were slow to adopt new ideas. Fasting was even more slowly adopted in America because at this time Benedict, Mendel, and others were claiming that fasting would increase keytosis, thus inviting coma, and therefore, it was dangerous. (29)

An American, Woodyatt, in 1909 wrote of semi-starvation for periods of from one to five days in the treatment of diabetes. Allen and Joslin further developed the fasting treatment. Allen in 1913, as well as, at the present time holds the view that diabetes is a disease of the total metabolism and not of carbohydrate alone. (28)

Let us now consider the pancreas as related to diabetes.

For through the study of this organ the most recent important progress has been made in the handling of the disease. Various and multiple have been the causes suggested for diabetes. A resume of the earliest history gives the following ideas as to the etiology: specific poison, remainder of an acute disease, cold and wet temperature and little resistance power of the surface arteries, drinking large quantities of water, and sexual excesses. Aretaeus believed it to be a form of dropsy; Galenus, and later, Paracelsus, pronounced the kidneys at fault, and Avicenna found the fault in the liver. The first mention of the pancreas made by anyone working along these lines was by Brunner in 1682. He removed the pancreas from fogs and produced a polydipsia and polyuria, but failed to interpret them.(16),(21)

Cowley in 1788 observed that diabetes may result from injury to the pancreas such as occurred when at the autopsy of one of his patients he found a stone in the pancreas. This fact was also overlooked in the annals of the disease.(10)

Langerhans (1869) described the islets in pancreatic tissue, and Cantanni held the view that atrophic changes in the pancreas were brought about by diabetes and that they were not to be considered as the cause of the disease.(9)

Lancerieux and Lapiere, Paris, (1877) claimed that there was atrophy of the pancreas in diabetes. Mehring and Minowski in Germany showed that pancreatectomy caused hyperglycemia, glucosuria and finally death.(51)

Vessale in 1889, ligated the common duct of Wirsung, noted that atrophy of the acinous tissue resulted, that no changes in the islets occurred, and that glucosuria was not produced. Therfore, he argued, the function of the islets

was apart from that of the acinous tissue.(6)

Lepine in 1892 believed that in diabetes the pancreas fails to produce the required ferment or internal secretion necessary for health. Williamson in 1894 suggested the implantation of living pancreas. Sandley in1894 suggested that a fresh extract of pancreas be injected, thereby hoping to replace the needed pancreatic ferment. Sir E. Sharpley Shafer in 1895 suggested that pathologic changes in the pancreas, in the islands may be responsible of diabetes. (32)

In America Opie in 1900 elaborated the idea that diabetes was a disease due to the degeneration of the islands of langerhans and that these islands had an internal secretion, that alteration of form and function in these structures resulted in diabetes, and that the acini of the pancreas were not envolved. (38)

Zuelzer, Dohrn, and Marxer (1906-1908) prepared an extract from expressed juice of the pancreas, treating it with alcohol and desolving the residue in salt solution or water . They noted the favorable effects of this extracr on the hyperglycemia of depancreatized dogs and also on the keytonuria of diabetes, and treated eight cases of human diabetes and four cases of keytosis with favorable results. The difficulty with their product was its impurity which after injection produced shivering, chills, and fever. Says Macleod in whose laboratories insulin was discovered,"There can be no doubt that Zuelzer in 1908 came very near to discovering the substance we now call insulin.(32)

Ssobelow and Schulze working independantly in 1902 found that after ligation of the excretory ducts of the pancreas, acinous tissue gradually undergoes atrophy, while the islands

remain intact. Their experiments also showed that withholding the internal secretion from the intestine did not produce glucosuria. He further proposed that if an extract of the islands obtained from a new born calf could be isolated such organotherapy might be effective in the treatment of diabetes. (43),(46)

Diamare and Kubabo in 1904 claimed the presence of a glycolytic ferment in the isolated islands of Langerhans of fishes. But as Allen says, the claims were overthrown by Rennie and then withdrawn by Diamare.(14),(4)

Messalgia in Italy in 1912 experimentally proved old facts about the pancreas and tried therapy with a pancreatic extract.(6)

Thus we see that some of the greatest minds in Europe had wrestled with the problem of diabetes, and, although the goal was all but reached, yet it remained for the young free blood of the Americas to grasp the final answer. The work of Opie in 1900 has all ready been mentioned. Allen in 1913, after surveying the entire field of diabetes and glucosuria, in his monograph, defined diabetes mellitus as, "the condition resulting from the reduction of pancreatic amboceptor below the requirements for normal metabolism". (4)

Banting: The underlying hypothesis underlying the experimental work of Banting was, according to his own writings formulated in November, 1920, after reading a report on Barron's work on the relations of the islands of Langerhans to diabetes. (32)

Banting's work began in November, 1920, in the laboratory of Professor Macleod, University of Toronto, Canada. Assist-

ing him was a student in Medicine, Best, and Collip, a biochemist. By May, 1922, the importance and possibilities of his extract Iseletin, now known as insulin, seemed very definite. Clinical application of the use of insulin was made by Cambell and Fletcher in the clinic of Graham, Toronto General Hospital.(9). Thus it was that insulin came into being.

Sir William Gull (1816-1890) one of Englands great physicians, physician to the Queen, is said to have been and extraordinary man/ It is said of him that he attracted many pupils and yet repelled many colleagues by his majesterial manner and temper. To a certain extent it may be imagined that he reflected the temperament of his day, when by his intolerant approach he said of Pavy,"What sin has Pavy committed, or his fathers before him, that he should be condemned to spend his life seeking a cure for an incurable disease"? In the light of what has happened ince the time of Sir William Gull it now appears that if there is anything in the history of diabetes which ought to be a source of deep satisfaction to Banting, Best, Collip, and Macleod, it should by this quotation from Gull. Insulin--Banting is the answer to Sir William Gull and to all of his kind who by some gross mistake find their way into medicine. And the remedy, insulin, whether for treatment or cure of an incurable disease, may well serve as an object lesson to all present and future workers in medicine.(6)

Banting, a young physician, demonstrator of physiology at Western University, London, Ontario was hither to unknown in the field of science. He had recently returned from the great war to his former work, and set out to find a remedy

for diabetes. Almost with one master strokehe touched the hidden spring which opened the door of discovery. Within a year the remedy which he deliberately sought was discovered. (6)

In these days when the world is in the shade of war clouds comes the thought that some scientists invent agents to destroy and others to preserve human life. It is 1,910 years from the time of Celsus, when he first prescribed for a diabetic patient to the time of Banting's discovery. The sum of human knowledge is built but slowly by the adding of human minds. Each man his tiny bit of intellectual energy adds to the problem till at last the shell of ignorance is blown apart and a new concept is born.

However wonderful isnulin is, and however grateful both patient and doctor are for having it, insulin alone is not sufficient. It is but half the buffer with which the ravages of the disease may be stayed. The patient's diet must be correct. Without proper diet insulin may become a useless and even a harmful drug. Joslin, more than any other of the really great American teachers has shown over and over again, to complete satisfaction that everyone from the age of twelve upwards can learn the simple arithmatic necessary for the calculation of a diabetic diet. He has also shown the way of educating the public by writing for the laity advising them in all phases of the disease from diagnosis and prohylaxis to treatment and prevention of the common complications of the disease.(27)

Now the problem is solved; the answer is known and the way clear for great alleviation of human suffering. It remains, however, a question to be answered as to how well

the knowledge gained will be used for its purpose. This purpose which is so often thwarted by human greed, selfishness, and human thoughtlessness.

In medicine we are forever gazing toward the horizon. It is inevitable that the acceptd ideas of one day should be replaced by the discoveries of the following day. History teaches man one lesson well, and that is, that man and his efforts are ever in transit. Man in his turn teaches history that within himself there is a procreant urge by which tomarrow must be made better than today. (6)

Bibliography

1. Adams, Francis; The Extant Works of Aretaeus the Cappodocian; London 1896; Printed for the Sydenham Soc.
2. Adams, Francis; The Seven Books of Paulus Aegineta; London 1844 Printed for the Sydenham Soc.
3. Allen, Fredrick M.; Scientific Progress in Diabetes; Hygeia 16; 496-498 1938
4. Allen, Fredrick M.; Diabetes and Its Treatment; Funk and Wagnalls Co.; N. Y. 1928.
5. Allen, Fredrick M.; Total Dietary Regulation in the Treatment of Diabetes; Rockefeller Institute 1919
6. Barach, J.H.; History of Diabetes; Ann. of Med. Hist. 10: 387-401.
7. Bauman, E.D.; History of Diabetes; Janus 37: 257-270.
8. Bles, Geoffrey; The Papyrus Ebers; C.P. Bryan, London 1930.
9. Campbell and Macleod; Insulin; Medicine Monographs; Williams and Wilkins Co.; Baltimore 1925.
10. Crawley, T.A.; A Singular Case of Diabetes; London Med. Jour. 9: 286-301 1788.
11. Cecil, Russel L.; A Textbook of Medicine; W.B. Saunders Co.; Philadelphia 1937.
12. Chatard, J.; Avicenna and Arabian Medicine; Johns Hopkins Hosp. Bull.; Mar. 1908-Dec. 1912; Reprints.
13. Cumston,C.G.ø History of Diabetes; Med. Jour. and Rec.; 120: 336-338.
14. Diamare, V. and Kuliabko, H.; Zur Frage nach der Physiologischen Bedeutung der Langerhansschen Inseln im Pankreas; Zentralbl. f. Physiol; 18: 432 1904-5.
15. Dublin, Louis I. and Lotka, Alfred J.; Twenty-five Years of Health Progress; Metro. Life Ins. Co. N. Y.

16. Foster, Sir Michael; Claude Bernard; Longmans Green and Co. N. Y. 1899.

17. Foster, Sir Michael; History of Physiology; Cambridge 1901.

18. Fulton, John F.; Selected Readings in the History of Physiology; C.C. Thomas, Baltimore 1930.

19. Garrison; History of Medicine; W.B. Saunders Co. Philadelphia 1921.

20. Guelpa, G.; Starvation and Purgation in the Relief of Disease; Brit. Med. Jour.; 2: 1050-1051 1910.

21. Horowitz, P.; History of Diabetes Mellitus; N. Y. Med. Jpur.; 111: 807.

22. Hemmeter, J. Conrad; Master Minds in Medicine; N.Y. Medical Life Press 1927.

23. Joslin, Elliot P.; A Diabetic Manual; Lea and Febiger Co., Philadelphia 1934.

24. Joslin, Elliot P.; Diabetes, Doctors and Dogs; Hygeia; 15: 168-170 1937.

25. Joslin, Elliot P.; Diabetes, Its Control by the Individual and tne State; Harvard Uni. Press 1931.

26. Joslin, Elliot P.; An Adress; Journal-Lancet; 16:129-31.

27. Joslin, Elliot P.; Treatment of Diabetes Mellitus; Lea and Febiger, Philadelphia 1928.

28. Joslin, Elliot P.; and Benedict, Francis G.; Metabolism in Diabetes Mellitus; Carnegie Inst. of Wash. 1910.

29. Kellog, P.M.; Guelpa's Discovery; N. Y. Med. Jour.; Mar. 1916.

30. Leopold, E. J.; History of Diabetes-Contributions of Aretaeus the Cappodocian; Ann. Med. Hist.; 2:424-435.

31. Lusk, Graham; The Elements of the Science of Nutrition;

W.B. Saunders, Philadelphia 1917.

32. Macleod, J. J. R.; The Antideabetic Functions of the Pancreas; C.V. Mosby Co.; 1923.

33. Magnus-Levy, A.; On Diabetic Acidosis; Johns Hopkins Hosp. Bull.; 22: 234 1911.

34. Mc Kettrick, Leland S.; Diabetic Surgery; Lea and Febiger, Philadelphia 1928.

35. Moon, R.O.; Hippocrates and His Successors in Relation to the Philosophy of their Time; Longmans N. Y. 1923

36. Naunyn; Der Diabetes Mellitus; Vienna 1898.

37. Noorden, Carl H. von; Disorders of Metabolism; E.B. Treat Co. N. Y. 1905.

38. Opie, E.L.; Diabetes Mellitus Associated with Hyaline Degeneration of the Islands of Langerhans; Johns Hopkins Hosp. Bull.; 12: 263-264 1901.

39. Pavy, Fredrick W.; On Carbohydrate Metabolism; J.A. Churchill, London 1906.

40. Pavy, Fredrick W.; Treatise on Foods and Dietetics; William Wood Co. N. Y. 1881.

41. Pussey, History and Epidemiology of Syphilis; Charles C. Thomas, N. Y. 1933.

42. Robinson, Victor; The Story of Medicine; New York 1931.

43. Schultze, W.; Die Bedeutung der Langerhansschen Inseln im Pankreas; Archiv f. Mik. Anat.; 44: 474 1900.

44. Sindoni, Anthony M.;:Diabetes; Mc Graw-Hill Co. N.Y. 1937.

45. Shaffer, P.A.; Antiketogensis; Jour. Biol. Chem.; 1922: 399-441.

46. Ssobelow, L.W.; Zur normalen und pathologischen Morphologie der Innersekretion der Bauchspeicheldrüse;

Virchow's Archiv; 168: 91 1902.

47. Stedman, Thomas L.; Twentieth Century Practice; William Wood Co. N. Y. 1895.

48. Stoddard, A.M.; The Life of Paracelsus; William Rider amd Son, Lltd. London 1915.

49. Trousseau, A.; Lectures on Clinical Medicine; Lindsay and Blakeston, Philadelphia 1873.

50. U. S. Department of Commerce, Bureau of the Census Mortality Stastics; 1911 and 1934.

51. Von Mehring and Minowski, O.; Diabetes Mellitus nach Pankreasextirpation; Archiv f. Exp. Path. u. Pharm.; 26: 371 1889-1890.

52. Warren, Shields; The Pathology of Diabetes Mellitus; Lea and Febiger, Philadelphia, 1938.

53. Webb, Gerald B.; Clio Medica, Tuberculosis; P.P. Hoeber,inc. N. Y. 1936.

54. Williams; History of Syphilis; Arch. of Path.; 13:779.

55. Wise, T.A.; A Review of the History of Medicine; Churchill, London 1867 Bk. 3.

56. Wyatt, R.B. Hervey; William Harvey; Small, Maynard and Co. Boston 1924.