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Some of the complicating factors of diabetes mellitus

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SOME OF THE COMPLICATING FACTORS
OF
DIABETES MELLITUS
BY
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I N T R O D U C T I O N

The Greek name diabetes means "running thru." In the second century A. D. Aretaeus the Cappadocian described it graphically as "A melting down of the flesh and limbs into urine; the patient never stops making water and the flow is incessant, as if from opening of aqueducts" (10). Galen compared the polyuria to diarrhea. He believed a similar condition existed in the kidney as in the bowel, thus permitting fluids to pass thru the body unaltered. Along with the rest of Galen's teaching this persisted until the end of the fifteenth century. In India as early as the fifth century the sweet taste of urine was described. Thomas Willis of England, 1679, called the disease the "Pissing Evil." One hundred years later Dobson recovered sugar from evaporated urine. A chemist, Chevreul, in 1815 proved that this carbohydrate was glucose. Diabetes Mellitus and Diabetes Insipidus were recognized and described as two separate entities by Cullen in the early nineteenth century. About one hundred years later, Von Mering and Minkowski proved that the pancreas produced a secretion, the absence of which resulted in incomplete carbohydrate util-

zation. However, it was not until thirty years later that Banting and Best working in the laboratories of McLeod prepared a pancreatic extract which was proved to contain the active principle and which became known as insulin. (10 and 15)

The disease is now recognized as an inheritable and constitutional disturbance. The impairment lies primarily in the pancreas with secretion of an inadequate (or possibly relatively ineffective, 3 and 5) supply of insulin. The polysaccharides, tetrasaccharides, trisaccharides and disaccharides of the diet are converted by the digestive enzymes (ptyalin of the *salivary* juice and amylase, amylopsin, maltase, lactase, and invertase of the pancreatic and intestinal juices) into monosaccharides which are absorbed by the mucosa of the small intestine. The monosaccharides are carried to the liver by the portal system where they are converted by glycogenesis into glycogen of the liver. As needed for metabolism by body tissues the store of liver glycogen is converted by glycogenolysis to glucose and is carried as such to them thru the intermediary, the blood stream. In the tissues, principally the muscle tissues, the glucose of the sys-

temic arterial blood is reconverted into muscle glycogen to be used immediately or later for the production of energy, thru the complex mechanism of metabolism. Insulin is the regulating factor. It increases the storage of liver glycogen and promotes the utilization of tissue glycogen.

The discovery of insulin by Banting and his co-workers has as Joslin (39) brings out introduced "a new race of diabetics." The unfortunate individual suffering from this disease is no longer dying of diabetes, but rather his death is usually due to some complicating factor.

The child who now develops diabetes can with careful and adequate supervision by his physician and co-operation on his part live a fairly normal and useful life. However, both parties because of his disease must be continually vigilant, for in the face of such complicating factors as infection, surgical problems, pregnancy, etc., his diabetes becomes a problem that is entirely different and by no means easy to control. As Conlin (21) states: "The diabetic's life expectancy depends upon his intelligence and the thoroughness of his training combined with the diagnostic and thera-

peutic skill of his physician."

In this paper it is my plan to discuss some of the complicating factors which endanger the life of the diabetic. In the time available it would be impossible to discuss all of these in their entirety. I shall, therefore, limit this paper to infections complicating diabetes mellitus, surgery complicating diabetes mellitus, and pregnancy complicating diabetes mellitus. The paper will deal with the effect that these complicating factors have upon diabetes, the dangers and prognostic outlook when they interrupt the diabetic's life, and the principles of treatment.

INFECTION AS A COMPLICATING FACTOR IN DIABETES
MELLITUS

While it has long been recognized that patients with diabetes mellitus succumb easily to other diseases, the part played by other infections in the course of a diabetic's natural life was little known before the discovery of insulin. In 1925, Graham (33) stated that before the introduction of insulin most diabetic patients died in coma without any other disease being detected in life or at autopsy. Since the advent of insulin, however, Graham states: "It has, therefore, been possible to watch patients for some days who would almost certainly have died very shortly after admission to the hospital unless insulin had been given. Under these conditions, the signs of another disease usually become apparent." As a result, therefore, of the discovery of insulin, our knowledge of the part that infections play as a complicating factor in diabetes mellitus has been greatly enhanced, and it is now a well known fact that infection may

hasten the development of, or even precipitate the disease or as stated so aptly by Biloon, Harris & Ringer (6), "It may precipitate the disease, it commonly aggravates the disease, and it often, through the intermediation of sepsis and coma terminates it."

"Adams," according to Conlin (21), "has shown that the onset of diabetes occurs more often in the fall, winter and spring, when infections are more common." Conlin further emphasizes this by stating that influenza was frequently given as an etiological factor in the six hundred sixteen cases studied at the University of Nebraska. "Stengel," quoted by Biloon, Harris & Ringer (6), "has reported five cases with definitely known non-diabetic history, who developed diabetes during the course of an acute infection." Maurer (48) states that Geyelen described eight patients who following the course of an acute infection developed a true diabetes mellitus. All eight were known non-diabetics prior to the onset of the acute infection. Biloon, Harris & Ringer (6) state: "Apparently during the course of an acute infection it is possible to develop Hyperglycemia, disturbances in liver function, inability to utilize injected insulin, and a full-blown diabetes." Wendt &

Peck (72) in their study of one thousand seventy-three cases of diabetes found that about four per cent of the patients prior to the onset of diabetes gave a history of tonsillitis. Spencer (63) remarks: "As a working rule do not think of infection as the cause of diabetes. Think of it, even in its least impressive form, as able suddenly to render florid a previously mild diabetes. The extraction of a tooth, a tonsillitis and a furuncle of the neck have led to a sudden unveiling of a diabetes so mild that it was not discovered previously, and now so severe that control is difficult." Conlin (21) is not of the opinion that infection is the etiological factor. However, he does believe that infection can precipitate the disease, especially in those individuals with a tendency toward diabetes. That infection can and does frequently aggravate the disease and often through subsequent sepsis and then coma terminate it, is also brought out by many other authors (13, 38, 75.)

There are many theories and hypotheses set forth in an attempt to explain the effect infection has upon the course of diabetes. None of these seem to fully answer the question. However, each is no doubt a building stone which in the future, and perhaps not too distant, will more or less lead to a final com-

prehension of the subject.

It is a well known fact that with the onset of an infection the glucose tolerance rapidly decreases and along with it the insulin rapidly becomes less effective, thus requiring tremendous doses of insulin to bring the blood sugar back to normal, even in the face of minor infections. Rabinowitch (56) believes that the severity of the infection has nothing to do with the degree of decrease in glucose tolerance. He states that he has seen in his experience furuncles and ordinary colds which have produced as great a disturbance as was found in more severe infections such as pneumonia, diphtheria, and the like. Maurer (48) states that infections anywhere in the body can lower the glucose tolerance. Biloon, Harris & Ringer (6) make the following statement: "It is, however, true that certain types of infection are more prone to reduce the glucose tolerance of diabetics than others. Infections of the respiratory tract and the gastrointestinal tract are notoriously liable to precipitate severe acidosis."

I will now present the various theories advanced by men working on this subject, in an attempt to find an explanation of how infection lowers so

quickly the glucose tolerance, and why insulin in a diabetic with infection becomes markedly ineffective.

Gilchrist and Wilson (31) in 1934 made the following statement: "In 1929 we published the fact that diabetes mellitus was curable by treating the etiological factor. We cited two cases and these are still cures and with normal glucose curves. Observation during intervening years has brought out the fact that in a large number of diabetic patients we were dealing with a staphylococcic factor in practically every case of focal infection in the upper respiratory tract." They then go on to explain that by removing these foci of infection by surgical procedures they were able to slowly cure their diabetic patients. Further, following the discovery of staphylococcic toxoid, which they felt would be a definite weapon to attack this etiological factor, they have proved to their satisfaction that diabetes in their region is due in a large percentage of cases to staphylococcic foci. By use of the toxoid they have been able to reduce in patients on insulin the daily doses of the latter. They believe that: "Insulin, which has saved so many lives by controlling hyperglycemia and glycosuria, nevertheless failed to produce cures, as

it did not treat the etiology. Staphylococoid toxoid because it reduces the toxemia which is producing hyperglycemia, is not only restoring blood sugars to normal but is uniformly doing the same with the other abnormalities which are present in the diabetic state."

Warren and Root (69) have described injury to island cells of Langerhans, which has occurred in acute infection, and they feel that this is due to the toxemia of such acute infections as pneumonia, scarlet fever, etc. They further feel that the transient glycosuria frequently seen in these acute toxic states is explainable on this basis and that the regeneration of the islet cells after the toxic state has disappeared explains the transient nature of the glycosuria.

Graham (33) advances the three following hypotheses in an attempt to explain the action of infection upon the diabetic patient: "(1) The infection may be a direct effect upon the beta cells of the islands of Langerhans, which prevents them from producing enough insulin to avert coma. Against this hypothesis as the sole cause is the observation that the amount of insulin required to lower the blood sugar of the comatose patients in whom an infection

was present was much greater than that required for the patient in whom no infection was even detected.

(2) The infection may cause an increased demand for insulin because of the increase in the metabolism.

Coleman and Dubois found that there was an increase of approximately forty per cent in the basal metabolism of patients in the third week of typhoid fever.

This increase in the metabolism would presumably entail the production of more insulin, but at present it is impossible to say how much more. (3) The in-

fection may destroy the insulin or form a substance which prevents it from acting properly. The large

amounts of insulin which were required to lower the blood sugar suggest that the insulin is less potent

than usual, but there is no direct evidence in favor of this." Some men (3,5) have shown that patients

dying in diabetic coma have an equal amount of insulin-like material in their blood and tissue juices as

is found in normal subjects. This they feel is strong evidence to support the theory that insulin is re-

duced in effectiveness rather than quantity.

Netzley (51) working along the same lines has shown in experimental animals (rabbits): "(1)

There is a rise in the blood sugar level of rabbits,

with the onset of symptoms of diphtheritic intoxication. (2) A rise in the blood sugar level of rabbits is coincident with the onset of an allergic reaction. (3) The blood sugar level is slightly lowered during an intense malarial paroxysm in man. (4) A reduction in the action of insulin occurs during diphtheritic intoxication in rabbits. (5) The blood sugar level remains normal in rabbits following the injection of a mixture of three minimum lethal doses of diphtheria toxin and 1/5th unit of insulin, when injected fifteen minutes after they are combined. (6) Insulin becomes less efficient, as determined by the blood sugar level of rabbits, when incubated with diphtheritic toxin for eighteen hours at 37 degrees C."

Tisdall (66) has shown that glucose when injected intravenously in the non-diabetic patient is removed less readily from the blood stream in the face of infection than when infection is not present.

Tallerman (64) has demonstrated that in acute infections the liver function, as estimated by the levulose tolerance, is definitely decreased.

Richardson (60) in studying immunity in diabetes says: "In this study, complement, natural

amboceptor and acquired amboceptor, as factors in the antibacterial power of the blood, have been investigated in diabetic and non-diabetic persons to determine whether this part of the protective mechanism of the blood is affected by the diabetes." From his studies he has drawn the following conclusions:

"(1) Complement in the blood of the diabetic patients does not differ in amount from that in the blood of non-diabetics. This is true whether or not infection is present. (2) The antibacterial power of the blood of diabetic patients as measured by standard methods tends to be less than that of non-diabetics. (3) Diabetic patients are less able than non-diabetic controls to form agglutinins following their inoculation with typhoid vaccine. (4) From these studies it appears that any deficiency in the antibacterial reactions of the blood of the diabetic comes rather from impairment of the amboceptor than from any lack of amount or activity of the complement. This is true of both the natural amboceptor and of the acquired amboceptor."

Rabinowitch (56) believes that in infection the endogenous insulin is decreased in amount and that the exogenous insulin is definitely less effec-

tive. This he believes might be due to an insulin destroying enzyme in the blood. He also states that fever alone is no doubt a factor in lowering the glucose tolerance. Lawrence and McCance (43) report a case which would indicate that the inhibition of insulin action by infections and sepsis is not due directly to the sepsis or toxins, but to the accompanying febrile reaction. They further suggest that increased action of the thyroid and adrenals (antagonists to the islet cells of Langerhans) may be more or less responsible for the increased demand for insulin. de Takatas & Fenn (22) made a similar observation in their paper.

Warren (68) believes that sepsis decreases the effect of insulin in maintaining a normal glycogen distribution. He further believes that the abnormal supply of glycogen in the tissues may be responsible for the increased susceptibility of diabetics to infection.

Burgers (11) makes the statement that hyperglycemia is the primary factor and most important in susceptibility to infection. He claims also that bacteria grow more readily in hyperglycemic blood. According to him such blood offers less resistance

to bacteria, especially to staphylococci, than does normal or hypoglycemic blood.

Infection, when it occurs in a diabetic patient, is to be handled and regarded with the greatest respect. That infection is the etiological factor is I believe a little far fetched. Nevertheless, it must be remembered that we must always be on the alert in those patients in whom diabetes because of heredity, obesity, age, sex, etc., might be expected; for as pointed out above, infection frequently precipitates the disease. The severity of the infection, other things being equal, apparently has little to do as far as its degree of effect upon the diabetic state. It has been pointed out that mild conditions such as furuncles, colds, tonsillitis, and other apparently mild infections do not infrequently precede the development of diabetes which may be quite severe, and furthermore, in patients who prior to the infection were known non-diabetics.

We know that sepsis and toxemia are factors in lowering glucose tolerance, and likewise in decreasing the effectiveness of insulin. It is mere conjecture only when we attempt to explain the mechanism of this. Perhaps the toxin in some manner

neutralizes the insulin. Another guess is that there is an enzyme in toxemia which destroys the insulin. However, all we really know is that the exogenous insulin is indeed less effective in the face of infection and one must therefore give tremendous doses of insulin in order to combat the hyperglycemia and subsequent acidosis and coma.

It has also been rather clearly shown that fever in itself can quite effectively lower glucose tolerance. Here we may be dealing with a factor which can be explained on a basis of increased metabolic rate, for it is a well known fact that metabolism is increased with each degree of fever. Hewlett (37) states that Dubois has shown that in fever there is an increase of 13 per cent in the metabolic rate with each elevation of one degree centigrade in the body temperature. Associated with an increase in temperature we also find an increase in the function of various endocrine glands, namely the thyroid and the adrenals. Therefore in that these two glands are antagonistic in function to the islet tissue of the pancreas we can readily see that they may play a definite part as regards the lessened effectiveness of insulin in infections.

A factor which I believe is quite important in throwing the glucose tolerance out of control is that the toxins produced by an infection are injurious to all of the tissue cells of the body. We know that degenerative changes occur both in the islet cells of the pancreas as well as in the liver cells during toxemia. Therefore it is not too difficult to conjecture that, with damage to the insulin producing cells of the pancreas and to the glycogen storing cells of the liver, the insulin will be reduced in amount, and further that the liver, because of this, as well as damage resulting from toxemia, will fail to properly store the glucose of the blood.

It must not be forgotten that the diabetic patient is also more susceptible to infection because of his lowered immunity, and because of the fact that bacteria grow more rapidly in hyperglycemic blood, thus is set up a vicious cycle. A diabetic is more susceptible to infection, and infection by increasing hyperglycemia and acidosis aggravates the diabetic state.

Numerous authors (28, 17, 23, 62, 25, and others) have recorded cases of diabetic patients

showing marked loss of glucose tolerance and insulin resistance with the onset of an infection of one type or another. Rabinowitch (56) states that of all conditions which render insulin ineffective and lower glucose tolerance, infection is at the top of the list.

What commonly happens is that the diabetic on insulin with the onset of an infection which may be only a mild upper respiratory thing loses his appetite, is unable to eat, and for this reason he omits his insulin, as brought out by Conlin (21), Duncan (23), Burgers (11), and others. This is the most dangerous thing he could do. The infection, as you have already gathered, rapidly raises the blood sugar and at the same time decreases the endogenous insulin in actual amount, as well as in its effectiveness. By not eating and by omitting his insulin the patient does two things: (1) He aggravates the diabetes, and (2) Lowers his defense mechanism to infection. Before the patient realizes what has happened and has called his physician hyperglycemia has become more marked, acidosis develops, vomiting may develop (producing dehydration and increased acidosis) and coma may be not far distant. All

diabetics should, especially when taking insulin, be instructed to call their physician and above all never omit, and perhaps better increase their insulin dosage with the development of any type of infection.

Not infrequently, when he first sees his diabetic patient who has developed an infection, the physician finds him in a precomatose or comatose state. As mentioned by various authors such patients may present the picture of an acute abdomen. Spencer (63) remarks: "Oftentimes the precomatose or comatose patient has a history of severe pain in the epigastrium or chest, shows an elevated temperature and pulse rate, vomits, and has a rigid tender abdomen and an elevated leukocyte count with a relative polynucleosis." He states that this leukocytosis resulting from acidosis and coma may reach figures as high as 25,000 to 30,000. He further emphasizes the importance of a careful history prior to the patient's development of coma, and states that in such cases the greatest degree of discretion and judgment is called for. Saunders (61), in a study of eighty patients found that this difficulty in diagnosis arose only in two instances. His impression is that simple diabetic coma of itself will not give the

symptomatology of an acute abdominal condition. Surgery in the diabetic without coma is serious enough, and one must not unnecessarily add additional hazards to the course of his illness. At the same time the physician must keep in mind that surgical procedures to eradicate foci of infection must if possible be carried out immediately upon indication. The physician who keeps in mind the fact that an acidosis or coma may simulate an acute abdomen may save his patient needless and unnecessary surgery.

Numerous writers have shown that by removal of foci of infection, or by curing infectious disease in the diabetic patient the physician is using his strongest weapon to combat hyperglycemia, acidosis, coma, and the lessened effectiveness of insulin. Rabinowitch (56) has observed that infection when eradicated leads to rapid recovery of glucose tolerance. Spencer (63) says: "Removal or drainage of a focus of infection frequently leads to a marked increase of carbohydrate tolerance." Biloon, Harris and Ringer (6) remark: "It is always our plan in the treatment of infection in a diabetic to control the infection rapidly by the necessary measures. If operative interference is required, we recommend it immediately

unless the general condition of the patient is such as to make hazardous the operative risk necessary to control the infection." Conlin (21) also emphasizes the treatment of infection as well as acidosis. Conlin has found infection responsible in about 60 per cent of (their) comatose cases at the University of Nebraska Hospital.

In treating the diabetic patient with infection the physician must not forget that he has other weapons to combat acidosis than by removing or eradicating foci of infection or by controlling infectious diseases. Conlin remarks, in speaking of diabetic coma: "All cases, therefore, should first be examined for infection and the treatment should be directed first toward that infection as well as towards the coma resulting from it." "Combating the infection, of course, is of the greatest importance, but at the same time, one can decrease acidosis by the use of insulin, carbohydrates, fluids, and possibly alkalies under the careful, watchful, and intelligent supervision of the physician, assisted by laboratory procedures and adequate nursing care."

In general authors are in agreement that enormous doses of insulin are required. Rabinowitch

(56) says that no routine course can be set forth in establishing the insulin dosage. Spencer (63) says: "Often huge doses of insulin must be used to relieve severe acidosis with coma, 150 to 200 units in 12 to 24 hours is usual. With infection the required dose tends to run higher. I have frequently used 300 to 400 units to bring a patient back to consciousness. The ideal method is to give frequent doses of insulin with as many grams of glucose as units of insulin. I am in the habit of giving part of the insulin by vein and part subcutaneously for the first dose or two, thereafter using only the subcutaneous route. I stay with the patient until consciousness is restored, taking blood and urine samples every two hours for quantitative or qualitative tests for sugar and acetone bodies. It takes little equipment to do these tests at the bedside." In treating a comatose patient Burgers (11) suggests the following rules: "Insulin 15 units every four hours - one-half hour after insulin give orange juice or oatmeal gruel (containing 15 grams of dry oatmeal) 4 ounces, force fluids. If urine shows green test reduce insulin to 10 units, if a blue test to 5 units. Resume dose of 15 units with yellow or red. Report nausea and vomiting. Keep fluid and urine chart.

After acidosis is overcome by this method the hyperglycemia may then be controlled by dietary and insulin adjustments." Conlin (21) says: "The dosage of insulin will vary with the case, the size of the patient and the duration of the acidosis. An initial dose of 30 to 40 units for the average adult followed every half hour depending upon urine tests is usually required."

One thing emphasized by some authors, and to be kept in mind, is that following the eradication of an infection the glucose tolerance rapidly returns to normal with associated return of effectiveness of the insulin. Unless this is remembered, as pointed out by Conlin (21), Spencer (63), and others, and the insulin dosage correspondingly reduced, the patient is apt to be thrown into hypoglycemic shock.

The literature is almost unanimous in agreement that in the face of infection a high carbohydrate intake is essential, as Conlin (21) remarks: "Fat and protein burn in the fire of carbohydrate, in the absence of carbohydrate they "smoke" and are burned only to the ketone stage - acidosis results." The supply of carbohydrate must therefore be kept up in order that the increased insulin may by burning carbohydrate reduce the formation of ketone bodies and thus combat

acidosis. The carbohydrate may be given by mouth in the form of orange juice, gingerale, oatmeal, and sugar, or intravenously in the form of glucose. The absorption of glucose by rectum is questioned by certain writers (49, 50, 54) and is perhaps not to be recommended. Certain writers, especially Spencer (63), use insulin in a glucose mixture when giving the latter by vein. This in selected cases is no doubt of considerable value.

Forcing fluids is essential to combat dehydration and the resulting and associated acidosis, and I found no authors who disagreed with this. Coburn (18) believes that by forcing fluids we not only combat dehydration but also assist the kidneys in excreting the acid products of impaired carbohydrate metabolism or ketone bodies.

The use of alkali to combat acidosis is indeed a much debated question. Joslin (39) and Reed (58) are of the opinion that it does no good and avoid its use. On the other hand such men as Bock, Fields, and Adair (7), Biloon, Harris and Ringer (6) and Campbell and MacLeod (14), are convinced that it is indicated in all cases of acidosis. It apparently does little harm, and it may or may not be useful in

reducing acidosis. From a physiological basis there is definite indication for its use. In the face of this disagreement in the literature, therefore, its use in my opinion is more or less discretionary.

All writers emphasize the importance of carefully watching the glycosuria, acid radicals (acetone and diacetic acid) of the urine, blood-sugar level, and carbon dioxide combining power of the blood in order to properly regulate the insulin dosage and carbohydrate intake (21, 62, 53, and others.) Certain men, namely Griffiths (35) and Appel and Cooper (2), have shown that in certain cases in which there is kidney pathology it is possible to have a diabetic acidosis with a negative test for sugar in the urine, and a positive test for ketone bodies. They also point out that glycosuria may be absent even in the face of marked hyperglycemia.

Numerous detailed outlines concerning the care of the diabetic patient in acidosis or coma can be found in the literature. They are all more or less alike and conform to the same fundamental principles. To present each in detail would only lead to confusion. I have, therefore, selected one which

I feel is quite satisfactory and present it here in detail as given by Biloon, Harris, and Ringer (6):

"Infection is the principle cause of coma in a diabetic. The central metabolic problem, therefore, in the management of a diabetic patient during the course of an acute infection is the control of acidosis and the prevention of coma. The treatment must, however, be directed at the same time against the infection since it is the direct cause of the acidosis.

At the outset certain elementary matters must be arranged. The patient must receive the general supportive treatment which is primary during the course of any acute infection. Specific treatment against the infection, if available, should be given immediately. Competent nursing attention is imperative in order to insure the proper regulation of diet and administration of insulin. In the absence of a competent nurse the physician should examine each voided specimen of urine himself for sugar and diacetic acid and give the insulin himself if the patient is not in the hospital.

Let us assume for example that a moderately severe diabetic is confined to his home, ill with an

acute infection of the respiratory tract with temperature, heavy glucosuria and ketosis. The general nursing care and medical treatment have already been secured, and the prevention of acidosis and coma concerns the doctor alone for the present. The solution stated very simply is this, the patient must burn 60 to 100 gm. of carbohydrate in twenty-four hours and must receive about 5 to 10 gm. of sodium bicarbonate daily while ketosis persists. Fluids in sufficient quantity to prevent dehydration have to be supplied.

Called to such a patient, with the problem presented, the first procedure consists in the giving of a dose of insulin subcutaneously (20 to 40 units.) Fluids in the form of milk, orange juice, broth, and coffee are to be given at two hourly intervals, 6 ounces at each feeding. Should vomiting occur proctoclysis of 5 per cent. glucose and 1 per cent. sodium bicarbonate solution must be promptly instituted, 500 cc. every six hours. This done the blood should be examined for CO_2 combining power if a laboratory is available. But treatment must never wait upon the blood examination unless there is a real diagnostic problem. If the clinical condition of the

patient becomes alarming as evidenced by increasing drowsiness and hyperpnea, another dose of insulin should be given. It is well to provide about 25 gm. of glucose in some form to cover each dose of insulin except the first. There is usually a marked hyperglycemia in impending acidosis, and even if the first dose is 40 units there is not much danger of too great a lowering of the blood sugar. In some clinics it is the practice to give insulin and glucose intravenously in cases bordering on acidosis or coma. We use the intravenous or subcutaneous route for glucose only as a last resort.

It is our practice to give small amounts of alkali by mouth or by Murphy drip to all patients with acidosis. Joslin, however, has not been giving alkali for many years, and due to the weight of his opinion the routine use of alkali is perhaps less general than its importance warrants. The deviation in normal metabolism, which is seen in any case of progressive acidosis in which the body excretes increasing amounts of ammonia and less of urea, points to the rational use of alkali. That in acidosis the alkali reserve of the body is depleted through combination with and excretion of newly formed abnormal acids is evidenced by the lowering of the CO_2

combining power of the blood, and is undisputed. Certainly then, on strictly physiologic grounds, there seems to be an indication for alkali in diabetic acidosis. The doses originally recommended, 6 to 8 gm. six times daily, were certainly too large and often made the patient very ill, and must have occasionally produced an alkalosis. Those patients with acidosis and coma due to the retention of organic acids other than the ketonic acids and those diabetic patients in whom the acidosis is the result not only of abnormal fat and protein burning but also of retention of acid metabolites due to a complicating nephritis certainly require alkali. One cannot combat these conditions with insulin and glucose alone.

There seems to us, therefore, to be no valid reason why alkali should not be routine in the treatment of diabetic coma. No harm can come from its use, since this use is based upon sound physiologic doctrine. No good can come from withholding it. It is true that often it is possible to control diabetic acidosis with glucose and insulin and without alkali. Joslin has given ample evidence of this. But this is not sufficient grounds for broadcasting the teaching that alkali must always be avoided in diabetic coma.

The amount to be given need not exceed 10 gm. in twenty-four hours (1 gm. alkali according to Woodyatt will raise the CO₂ combining power of the blood 1 volume per cent. in a man weighing about 85 lbs.) Thus with a low CO₂ to start with, no harm can possibly come from a rise of 10 volumes per cent. And even when given on top of a normal CO₂ combining power (45 to 50 vol. per cent.) no alkalosis can possibly intervene with the dose.

With the subsidence of the toxemia and drop in temperature without the development of acidosis it is safe to allow a soft and easily digestible diet containing milk, cereal, toast, eggs, and clear broth. Never curtail carbohydrates while the patient is still sick with acute infection. It is only necessary to make carbohydrate burn in sufficient amounts to render normal the burning of fat and protein. This can usually be done by the use of insulin. It is always wrong to give large quantities of vegetables to diabetic patients ill with fever. It is not safe to attempt to control glucosuria and hyperglycemia by dietary regulation until the acute illness has passed. During the period of severe illness, however, it is well to have a constant moderate glucosuria in each voided or catheterized specimen. In this way chances for hypoglycemic reactions are reduced to a minimum.

Once the infection is under control the danger from acidosis is decreased, and with hyperpnea and drowsiness no longer present, supervision of the patient may be somewhat relaxed. A balanced diet can then be arranged to contain vegetables and sufficient protein to insure nitrogen equilibrium. All the urine should be saved in twenty-four hour specimens, and enough insulin given in divided doses to control the glucosuria. It is to allow 1 unit of insulin for every 2 gm. of sugar in the twenty-four hour specimen of urine."

S U M M A R Y

By the use of insulin the life span of the diabetic has been increased. This has made it possible to study these patients over a longer period of time with more care and thoroughness, thus giving us a better and more accurate comprehension of the subject.

It is fairly well established that infection can in certain individuals predisposed to diabetes usher in the disease which may be quite severe. This is borne out by the frequency with which diabetes follows closely or immediately upon acute infections which may be only a cold, tonsillitis, or a more

severe infection such as diphtheria, scarlet fever, etc. Further, it has been shown by some men that the onset of diabetes is more common during fall, winter, and spring when upper respiratory infections are more common.

That infection is the etiological factor is I believe rather out of order. The primary lesion is in the islet cells of the pancreas. However, infection by some mechanism does precipitate and does aggravate the diabetic state.

The septic and toxic state associated with an infection are apparently definite factors in the development of or aggravation of the diabetes. This may be due to the degenerative changes in the islet cells resulting from the toxemia, thus reducing insulin quantitatively. Another possibility is that the toxin neutralizes the insulin and/or possibly in toxemia there is an insulin destroying enzyme. It may be added that infection even in the non-diabetic reduces the sugar tolerance and further the effectiveness of insulin.

Fever is also a definite factor in aggravating the diabetic state. Here we may be dealing with an increase in metabolic rate associated with

increased activity of the thyroid and the adrenal glands known antagonists to the islet cells.

The high glycogen content of the diabetic's blood stream favors the growth of bacteria. Further the diabetic's natural and acquired immunity is definitely less than that of the non-diabetic. Thus the diabetic state invites the development of infection which in turn aggravates the diabetes -- definitely a vicious cycle.

With the development of an infection the diabetic's glucose tolerance is rapidly and markedly reduced and insulin, both exogenous and endogenous, becomes relatively ineffective. However, with the removal or cure of the infection the patient almost as quickly regains his glucose tolerance and insulin again becomes effective.

A diabetic taking insulin should never omit his insulin in the face of infection, even though he is unable to eat. Further he should take some form of carbohydrate equivalent to that of his diet and should call his physician under all circumstances. By failing to do any or all of the above three he simply invites the rapid development of a more severe infection and a dangerous diabetic state which may

go as far as acidosis and coma or even death.

The physician must keep in mind that the diabetic in coma may simulate an acute abdomen. The occurrence of this is, of course, rare, but to operate needlessly upon a comatose diabetic for a condition not existing would only be inviting trouble.

In treating the diabetic with an infection one must remove or cure the infection as quickly as possible. He must give large doses of insulin and high carbohydrate carefully regulated by frequent urinary tests for sugar, acetone, and diacetic acid, and blood determinations of blood-sugar levels and carbon dioxide combining power. With the removal of the focus of infection the tolerance rapidly returns to normal, thus requiring less insulin. To forget this might lead to disaster. In combating the acidosis one should also force fluids and use alkalies. Careful nursing care with skillful and thorough attention on the part of the physician are essential.

Last but not least the diabetic should be told of his increased susceptibility to infection and carefully instructed as to how best to avoid the development of infection and warned to call his

physician immediately when this occurs. The prevention of complicating factors is by far better than their cure.

SURGERY AS A COMPLICATING FACTOR IN DIABETES
MELLITUS

With the discovery of insulin the life of the diabetic assumed a totally new and brighter outlook. No longer did his physician tag him as a hopeless case. On the contrary his life expectancy under intelligent supervision and unwavering co-operation on his part became almost equivalent to that of the non-diabetic. However, with this increased span of life, other complicating factors were added to discourage the diabetic bolstered up by Banting's and Best's gift. Surgery was not least among these. Conlin (21) remarks: "One out of every 3.2 of our patients has a surgical complication, but one of every two surgical patients will require surgical treatment of some kind before he dies. The lives of the surgical diabetics have been prolonged since the advent of insulin due to a greater knowledge of the problem and a closer co-operation between internist and surgeon." As Mason (47) says: "Today with our better understanding of the disease, and with insulin, has the situation changed? Death from diabetic

coma per se is becoming more and more infrequent while the various surgical complications are rapidly assuming major importance as the cause of death in diabetes." Hauser and Foster (36) vividly contrast the surgical prognosis of a diabetic thirty years ago. They pointed out that at that time surgery was used only as a last resort in the presence of diabetes, while now no diabetic is denied surgery because of his disease.

Before 1922 surgical procedures upon diabetics were attended with much anxiety and fear. Mason (47) says: "Formerly the diabetic was a notoriously poor surgical risk." He presented statistics on 101 diabetic patients who were operated between 1916 and 1924 at the Royal Victorian Hospital. In a group of 41 patients who had surgery prior to 1922 there were nine deaths, a mortality of 22 per cent. Those cases operated upon since 1922 (61 patients with nine deaths) showed a mortality of 15 per cent. Gager (29) concludes: "Now after a widespread trial of insulin, it may fairly be said that by its use, supplementary dietary regulations, the surgical hazards peculiar to diabetes have been overcome." Fitz and Murphy (26) are of the opinion

that the death rate in diabetics undergoing surgery has been reduced to one-third by the use of insulin. Ralli and Standard (57) aptly say: "The diabetic patient should not be denied surgery because of his diabetes. Properly treated he will prove a safe surgical risk. With this in mind surgery in the diabetic should be extended beyond the limited scope of emergency life saving operations. He should be accorded surgery that not only saves his life but also makes life more livable. A hernia or a relaxed perineum may be repaired, an infected gall bladder drained or removed, and a chronic or acute appendix removed as in any other person. In acute infections, surgical interference is particularly indicated in patients with diabetes. Infection is a serious menace to the diabetic patient, so increasing the severity of his diabetes that he may readily go into coma. The diabetes in such cases is an added indication for the removal of the infected part."

What is the prognosis of the surgical diabetic patient today? Ralli and Standard (57) found a mortality of 16.4 per cent in 96 diabetics operated upon between 1930 and 1934. Rabinowitch (55) found that there was no appreciable difference in

the mortality or morbidity of fifty diabetics who received surgery for gall bladder disease as compared with a similar non-diabetic group. He feels that with proper preoperative, operative, and post-operative care the recommendation of surgical treatment of gall bladder disease is justified. White (73) in a study of the records at the Roosevelt and New York Hospitals found still more encouraging statistics. His studies revealed a mortality of 2.8 per cent as compared to 40 per cent prior to 1922. Bazin (4) in comparing the surgical mortality of diabetics and non-diabetics since the introduction of insulin found 2.74 per cent and 2.44 per cent respectively. Weeden (70) had a pre-insulin mortality of 36.6 per cent and since insulin has had only 16.6 per cent. Coley (19) however found from 1926 to 1927 a surgical mortality of 33 per cent in 39 cases which were operated at the Lincoln Hospital. Joslin (39) reports a pre-insulin mortality of 13.5 per cent with 11.5 per cent since the discovery of insulin.

The consensus of opinion among the various authors leads one to feel that the diabetic when in need of surgical attention should be granted this

privilege. Surely one would not deny the diabetic surgery that will promptly remove a focus of infection. This paper has already shown that foci are not infrequently responsible for greatly increasing the severity of the diabetes, and further that their prompt removal if surgically possible is necessary and often life saving. Gager (29), Coley (19), and Bothe (8) and others have vividly shown that the diabetic toll is decreased by the early surgical removal of foci of infection. Furthermore, as has been suggested and will be brought out more clearly later, the diabetic should be allowed surgical treatment of complications, which though not endangering his life do definitely make him uncomfortable. Herniorrhaphies, removal of tumors, plastic surgery, etc., can with adequate pre-operative, and postoperative attention be carried out with no more danger to the life of the diabetic than when carried out in the non-diabetic.

Of the complications which endanger the diabetic's life during surgery acidosis and coma come first, while failure of surgical wounds to heal and infection of surgical wounds are no doubt second. Another factor of major importance and one that must never be forgotten when doing surgery, especially

on the older diabetics, is the diffuse arteriosclerosis. Ralli and Standard (57) emphasize this when they say: "The cause of death following surgery in the aged diabetic is not primarily due to a disturbed carbohydrate metabolism, but rather to the diffuse arteriosclerosis. This may involve all their vessels, cerebral, coronary and renal as well as those of the extremities. Only those of the extremities are amenable to surgical treatment and the diffuse vascular inadequacy is still beyond our scope. Their death is often one of circulatory failure, kidney insufficiency, or cerebral accident."

In the treatment of the surgical diabetic prophylactic measures must be taken to avoid acidosis and coma. Foster (27) believes that every patient with diabetes, who is operated on, should be regarded as a candidate for coma, and that its prevention is better than its cure. This can be accomplished, as pointed out by nearly all writers on the subject, by using preoperatively a high carbohydrate diet and/or glucose intravenously with sufficient insulin to split the carbohydrate, thus tending to keep the blood sugar within nearly normal limits and the urine almost sugar and acetone free. Terry (65) also

believes that small quantities of alcohol should be given, for according to him, it is very effective in building up the supply of liver and tissue glycogen. He as well as others (27, 1, 76, 52) point out that preoperatively with such a high carbohydrate intake there may be traces of sugar in the urine. However, this is rather to be sought for than avoided, for with adequate insulin the patient with a rich supply of glycogen is less apt to develop acidosis or coma during or following the surgical procedure. High carbohydrate intake with adequate insulin does two things: (1) It burns fats thus preventing ketosis and acidosis, and (2) It builds up the supply of glycogen within the liver and other tissues of the body.

When considering the surgical diabetic, one, as pointed out by various authors (29, 44, 45, and 19), can divide them into two groups: (1) Those under elective surgery, and (2) Those under emergency surgery. In the former group the results are more satisfactory, for here there is no special hurry in carrying out the surgery. The patient who comes in for a tonsillectomy, the removal of a chronic appendix, or tumor and the like can be carefully

preoperatively prepared by an internist, with high carbohydrate intake and adequate insulin so as to render him relatively free from acidosis and at the same time build up his glycogen supply. The patient who comes in for emergency surgery, however, presents a problem somewhat different. In his case there is pending or actually is acidosis. Here vigorous steps with high carbohydrate and sufficient insulin must be given; and if the loss of tolerance is due to infection, this must, as already emphasized, be promptly removed if surgically possible.

The treatment of acidosis or coma is the same here as discussed in detail under infections and need not be repeated.

The anesthetic for the diabetic must be selected with much care. Leonard (44) believes that anesthetics affect the diabetic as follows: "(1) Inhibit insulin activity, (2) Reduce glycogen in liver, (3) Reduce glycogen in voluntary muscles and heart, (4) Inhibit the formation of glycogen from lactic acid in muscle, and (5) Cause breakdown of lactic acid precursors in muscle, yielding lactic acid and phosphoric acid, thus accounting for part of the acidosis. Anesthetics inhibit the oxidative

enzyme system of the brain dealing with glucose and lactic acid in direct proportion to their narcotic potency. According to Leake, the deeper the narcosis under an anesthetic agent, the greater the inhibiting of the oxidative enzyme system dealing with glucose and lactic acid except in the case of morphine narcosis. Ether while tending to produce postoperative acidosis is not definitely contraindicated, if careful attention is paid to preoperative care. The most satisfactory policy is to use the anesthetic which will make the work of the surgeon easiest and safest."

Ralli and Standard (57) remark: "As to anesthetics, the most desirable is the one that leaves the patient conscious following the surgical procedure. Any anesthetic that tends to produce liver damage is particularly to be avoided. This means specifically chloroform, and to a somewhat lesser degree, ether." Bothe (8) believes that ether is contraindicated because it produces hyperglycemia, disturbs respiration, and postoperatively there is nausea and vomiting. Most authors (for example 30, 57, 76 and 9) are in agreement that chloroform and ether are definitely contraindicated.

In some cases where there is an adequate glycogen supply and where sufficient relaxation cannot be obtained with other anesthetics, gas oxygen supplemented by ether can be used. When doing so it is important to remember that following the anesthetic, the use of 5 per cent carbon dioxide with oxygen is of definite value in removing the ether and combating acidosis. Leonard (44) aptly remarks: "Frequently gas has failed to give complete relaxation and small amounts of ether are substituted. If the system is saturated with ether, carbohydrate metabolism is retarded and the effect of insulin may be neutralized. However, in such cases, where it has been necessary to give ether to get complete relaxation, the system may be rid of ether by the inhalation of five per cent carbon dioxide in air or oxygen after operation."

The anesthetics of choice are:(1) Local or spinal block, (2) Gas, including nitrous oxide, ethylene, and cyclopropane, (3) Avertin, and (4) Gas ether. These should all be supplemented pre-operatively with morphine and scopolamine or with one of the barbiturates. (44, 76, 57, and others.)

Numerous detailed outlines may be found

in the literature suggesting preoperative, operative and postoperative treatment of the diabetic subjected to either elective or emergency surgery. They are all fundamentally alike. The following has been suggested by Terry (65):

"A. Chronic Cases: (elective surgery)

The day before operation: Regular diabetic diet covered by insulin so as to make sugar free or nearly so. Do not lower blood sugar quickly, especially in old arteriosclerotics, and do not aim for too low blood sugar before operating. Diabetics stand surgery better with a fair amount of blood sugar - 150 to 200 mgms. is probably ideal. This is frequently associated with faint traces of sugar in the urine - cloudy green reductions, or even a little orange color.

The day of operation: Fluids - broth, tea, coffee, and water - are forced until two or three hours before operation. Usually no insulin before operation if sugar and acidosis are controlled. If not controlled, treat every hour or every two hours by orange juice or ginger ale (6 ounces) and insulin according to color formula in urine - 15 units if red reduction, 10 units if yellow reduction, 5 units if

green reduction, until controlled. If this method does not control acidosis, then treat as in acute cases, as gastric absorption may be delayed due to nervousness. Orange juice taken two or three hours before operation may be vomited unchanged during operation.

Postoperative: 50 grams of glucose in 1000 cc. saline in operating room, or as soon as patient has reached his own room, together with insulin - 20 units subcutaneously. One hour later, 5 or 10 units of insulin according to the severity of the case. Patient should be catheterized and specimen discarded as quantity of sugar due to usual spitting immediately following infusion may be poor index to insulin dosage, permitting too much insulin and consequent hypoglycemia. Two hours later, insulin 15, 10 or 5 units according to color formula in urine probably catheterized. Four hours later, repeat urine and insulin according to color formula. Six hours later, carbohydrate is begun by mouth with insulin p.c. according to amount taken and color formula in urine.

An example: Gruel - 4 oz. (carbohydrate 12) or gingerale - 6 oz. (carbohydrate 10) - insulin 5, 10

or 15. Repeat every 2 hours until regular or soft diet with insulin to cover. If not taking fluid by mouth six hours postoperative, repeat glucose by vein with insulin. 100 grams of carbohydrate by mouth or vein each twenty-four hours postoperative. May continue 50 grams of glucose in saline by vein with insulin regime. B. D. ad lib if necessary because of vomiting or acidosis. Watch and wash the stomach.

B. Acute Cases - Dehydration, Vomiting and Acute Infections (emergency surgery)

Surgical success depends on early operation. Don't wait for ideal conditions. Best treatment for acidosis is removal of infection. Usually cannot get sugar-free or low blood sugar.

Surgical Diabetic Regime - Preoperative: Wash out the stomach in acute abdominal cases or any severe acidosis. Give 20 units of insulin subcutaneously and 50 grams of glucose in 1000 cc. saline and go ahead.

Postoperative: Treatment same as that given for chronic cases except that more fluid may be given by vein or additional saline subcutaneously. Rectal absorption doubtful.

Twenty-four Hours Postoperative: Liquid diet ad lib with insulin and food according to color formula - gingerale, tea with or without sugar, broth or gruel preferable to orange juice.

C. All Cases:

All cases are treated according to severity, mild cases and minor surgery requiring only small amounts of insulin with glucose by mouth before and after operation.

Blood Sugar: Preoperative ideal: 150 to 200.

Postoperative ideal: 110 to 160 because infections heal better with a low blood sugar.

Urine: Preoperative ideal: few tenths of glucose.

Postoperative ideal: sugar free.

Anesthesia: Coma in surgery may be caused by chloroform, too much ether, restriction of carbohydrates and water. Spinal anesthesia, gas and oxygen, or ethylene gas are probably best.

Exercise: In bed as soon as possible, out of bed as soon as permissible.

Sedatives: A restless patient probably needs fluids or glucose. Better restless upstairs than at rest downstairs."

S U M M A R Y

The diabetic's life span was definitely increased by the use of insulin, but at the same time the otherwise bright outlook was marred by the increased frequency of complicating factors. Surgery was one of the major intruders.

Prior to insulin the diabetic was subjected to surgery only as a last resort. This was because of the high mortality associated with surgery in the diabetic. By the use of insulin the mortality of the surgical diabetic has been reduced from around twenty-five to thirty per cent (pre-insulin mortality figures given by various authors range from fifteen to forty per cent) prior to 1922 to ten to fifteen per cent (various authors present figures ranging from three to fifteen per cent) since insulin has been used.

At the present time a diabetic with adequate preoperative, operative, and postoperative care can undergo elective surgery, herniorrhaphy, plastic surgery, etc., with perhaps as good a prognostic outlook as his non-diabetic brother. Emergency surgery which deals principally with eradication of foci of infection should be carried out as early as possible.

These foci are frequently the factors which are responsible for the diabetic patient's loss of glucose tolerance. By their removal the tolerance is quickly regained, thus making surgery almost a necessity. The earlier such foci are removed the better the prognosis.

The complications arising in a diabetic subjected to surgery are first, acidosis and coma. By the use preoperatively of high carbohydrate by mouth or intravenous glucose with adequate insulin the incidence of coma is decidedly reduced. It is apparently the best policy to force preoperatively carbohydrates and possibly small doses of alcohol with adequate insulin to the point that the urine shows traces of sugar with a slightly elevated blood-sugar level, for apparently with such a rich glycogen supply in the liver and other tissues the possibility of acidosis developing during or after surgery is then decidedly reduced. Postoperatively one should attempt to keep the blood-sugar normal or slightly below normal and the urine sugar free, for apparently wounds heal more readily and infections (the second group of complications) are least apt to occur. The third complication is

the diffuse arteriosclerosis, especially of the older diabetics, and is still our most serious problem. As yet we have no weapon to attack it. The surgical diabetic thus is more apt to die a cardiac, renal, or cerebral death than from some other complication.

Anesthetics by inhibiting insulin action, by reducing liver and tissue glycogen, by impairing glycogen metabolism (formation of glycogen from lactic acid in muscles), by disturbing respiration, and by postoperative nausea and vomiting lead to hyperglycemia, incomplete carbohydrate metabolism with the production of ketone bodies, and impaired elimination of acid radicals by the lungs and kidneys with the subsequent development of acidosis and coma. The worst offenders are chloroform and ether. The former is never to be used. The latter in selected cases, with high glucose content of the liver and other tissues and where other anesthetics do not give sufficient relaxation, may be used to supplement gas. When doing so, the patient should be given postoperatively carbon dioxide and oxygen to facilitate the removal of ether. The anesthetics in order of choice are: (1) Spinal block

or local, (2) Gas, including nitrous oxide, ethylene, and cyclopropane, (3) Avertin, and (4) Gas ether.

PREGNANCY AS A COMPLICATING FACTOR IN DIABETES
MELLITUS

Women who have diabetes are less apt to become pregnant than their non-diabetic sisters. Prior to Banting's and Best's remarkable contribution pregnancy was rare in the diabetic woman. For as pointed out by Parsons, Randall, and Wilder (53) and others, amenorrhea and sterility apparently due to failure of ovulation was the rule. Further, they pointed out that vulvitis, vaginitis, and cervicitis were common in the diabetic and were perhaps factors in sterility. They said that it was doubtful whether patients with diabetes even survived pregnancy in the pre-insulin days. Another factor as pointed out by Kramer (40) is that the diabetic before the introduction of insulin did not as a rule live long enough to become pregnant.

Since 1922 the frequency of pregnancy in diabetic women has changed, however, it is still quite uncommon. Parsons, Randall, and Wilder (53) found since 1922 only eleven pregnancies in 285 diabetic women. They quote von Norden as having

reported 22 in 427. Duncan and Fetter (24) remark: "There was not a single instance of diabetes in 27,567 consecutive patients confined in the City of London Maternity Hospital." Kramer (40) found an incidence of about one diabetic in one thousand pregnancies. He, however, points out that there has been a steady increase. In 1923 he found three cases with the number of pregnancies gradually increasing to the forties in 1931, and in 1934 to the fifties.

From the literature it is quite difficult to set an exact figure as to the frequency of pregnancy in diabetic women. However, this much is certain, although pregnant diabetics prior to 1922 were extremely rare, they have since then gradually become more common. This increase no doubt is due to the use of insulin which has increased the diabetic's life span and further has with the control of his diabetes improved the physiological function of other systems of the body. As Lawrence (42) points out, insulin has improved menses and fertility with a corresponding increase in frequency of pregnancy in diabetics. Parsons, Randall, and Wilder (53) remark: "With the

introduction of insulin the treatment of diabetes improved so much that prognosis of pregnancy and diabetes should now be improved. This is to be hoped for, especially because the incidence of pregnancy in diabetic women is likely to increase. Amenorrhea is an infrequent occurrence in patients receiving adequate early treatment and vulvitis, vaginitis and cervicitis are seldom if ever found if glycosuria is controlled."

Diabetes has a very definite effect upon the development of the fetus. Perhaps the most striking is the change which occurs in the product of gestation. Gordon (32) after studying the pancreatic tissue of babies born of diabetic mothers, dying in hypoglycemic shock concludes: "The pancreatic tissue from all babies showed an enormous hypertrophy and hyperplasia of the insular tissue. In the islands the individual cells were large with abundant cytoplasmia, and markedly increased in number, resulting in increase in the size of the islands, in some instances as much as six to eight times the average diameter in the normal newborn pancreas. The islands were increased in number. In some areas approximately fifty per cent of the

tissue was insular tissue. In and about the islands was an abundant infiltration of eosinophiles which in some areas between the islands was so extreme that more than fifty per cent of the cells were eosinophiles." Duncan and Fetter (24) found at necropsy a remarkable hypertrophy and hyperplasia as well as an increase in number of islet cells in the pancreas of the child born of a diabetic mother. Collins and Schack (20) say: "That there is a hyperplasia of the island cells is a well known fact." Gray and Feemster (34) have reported an autopsy in a child dying shortly after delivery which showed marked hypertrophy and hyperplasia of the islet cells. In fact they found that it was twenty-four times that of the pancreas of the normal child. Carlson and Drennan (12) have shown in experimentally depancreatized pregnant bitches that the diabetes develops not during the period of gestation but rather following the delivery of the products of pregnancy. These facts definitely point to increased activity of the fetal pancreas, to supply not only the insulin necessary for its own metabolic processes but, further, that for those of the mother.

Nearly all authors agree that this hypertrophy and hyperplasia of the pancreas of the fetus is due to the increased demand on the maternal side. Apparently the hyperglycemia of the maternal blood and likewise of the fetal blood affords a stimulus to increased activity of the islet cells with subsequent hypertrophy and hyperplasia of the fetal pancreas in order that it might meet the added demand for insulin. Collens and Schack (20) aptly describe this: "Our own recent published experiments appear to confirm the observations of Staub that a plethora of glucose in the blood stimulates insulin function. It seems likely on the basis of these observations that the high glucose concentration of the fetal blood maintained as it is by its constant supply of maternal blood has a stimulating effect on the island cells of the fetal pancreas. It is reasonable to assume that the constant stimulation of the islands by a persistent hyperglycemia results in the hyperplastic picture."

As can readily be seen after the above discussion, the baby born with a hyperplastic and hyperactive pancreas will with the removal of his diabetic mother's reservoir of hyperglycemic blood

rapidly go into hypoglycemic shock. This is also pointed out by Gordon (32) and Duncan and Fetter (24).

The hyperglycemia and associated insulin secretion naturally speed up metabolism with the subsequent development in utero of abnormally large babies as is pointed out by Kramer (41), and Gordon (32) and others.

The chances the diabetic mother has of giving birth to a live and well child are decidedly less than in her non-diabetic sister. Abortions both spontaneous and therapeutic, miscarriages, stillbirths, or deaths shortly after delivery are by no means uncommon. Parsons, Randall and Wilder (53) report four miscarriages and two stillbirths in eleven diabetic women who became pregnant. Kramer (40) in 355 cases found that 223 cases went to term, 49 had spontaneous abortions, 37 had therapeutic abortions, and 46 had premature births. In other words 132 or 30.9 per cent failed to go to term. Skipper (77) gave an account of 24 diabetics complicated by pregnancy in which there were four therapeutic abortions, one spontaneous abortion, and three stillborn macerated fetuses. McIlroy, Hill, and

Pillman (77) reported one stillbirth in eight pregnancies. Reveno (59) reports a diabetic patient who following several miscarriages gave birth to a child who died shortly after delivery. Weiner (71) reports a diabetic mother who gave birth to a dead child. Kramer (40) emphasizes this when he says: "There is an increased liability assumed by the mother in undertaking pregnancy. There is a strong probability of the pregnancy not reaching term. Chances of a live baby cannot be assured. In order to obtain the best results the patient must faithfully carry out the treatment as outlined."

The effects of diabetes upon the course of the pregnant mother are also of considerable importance. Kramer (40) found in his study of 665 cases that coma was present in 61 cases or 9.1 per cent. He says that it usually makes its appearance in the later months and comes on suddenly. Acidosis was found in six cases or 1.4 per cent. The lower result here he believes can be attributed to the fact that all or nearly all of the cases of coma were due to acidosis. Hydramnions were found in eighteen cases or 4.2 per cent, toxemia in twelve cases or

2.8 per cent. He remarks: "Besides commonly accepted conditions such as acidosis and coma, hydramnions, and toxemia it is doubtful whether diabetes exerted much influence upon the development of complications." "Williams and Offergeld," quoted by (53), "report twenty-five to thirty per cent of diabetics have died of coma shortly after delivery, others died of infections, while others died because a mild diabetes became worse." McIlroy, Hill, and Pillman (77) found in eight cases which they reported, no cases of sepsis and there were no maternal deaths. Kramer is of the opinion that the liability of the diabetic is ten times that of the non-diabetic.

As has already been shown, the child of the diabetic mother may be of abnormal size. With this in mind it is not too difficult to assume that labor because of disproportion between the maternal canal and the passenger may be very difficult and prolonged. This in the diabetic patient, especially if the disease is severe, can lead to serious consequences.

Lactation in the diabetic mother has come up for considerable discussion. Chaikoff and Lyons (16) working with experimental animals believe that

they have demonstrated that the lactation hormone of the anterior pituitary gland is ineffective in depancreatized dogs when on adequate insulin. Markowitz and Soskin (46) have observed that pregnant depancreatized dogs maintained on insulin failed to show mammary hypertrophy or lactation following emptying of the uterus. This was also observed by Chaikoff and Lyons (16). Tolostoi (67) remarks: "Five diabetic lactating women were studied to determine whether a quantitative relationship exists between the concentration of glucose in the blood and of lactose in the milk. The blood sugar was elevated by means of glucose ingestion and lowered by varying doses of insulin. It was found in every instance that the concentration of lactose in milk remained remarkably constant in spite of very marked elevations or depressions of the blood glucose concentration."

From these observations it would seem that the nursing of a child by a diabetic mother is contraindicated. Certainly if the lactose content of the diabetic mother's milk is not affected by the glucose concentration, then removal of glucose to synthesize milk especially if blood sugar is low, would

be a serious thing in a diabetic mother. In a series of eight pregnancies presented by McIlroy, Hill and Pillman (77) all the babies were artificially fed. Kramer (41) remarks: "With the onset of lactation the blood sugar drops thus requiring a decrease in insulin dosage." He believes that it would be to the mother's advantage if the responsibility of breast feeding could be obviated.

The effect that pregnancy has on the diabetes is indeed a somewhat debated question. Perhaps this can be explained by the fact, as previously pointed out, that pregnancy in diabetic women is indeed rather uncommon.

Wilder (74) has reported a case which required insulin during the first trimester. During the last trimester the patient did not require insulin, but it had to be resumed again after the patient stopped nursing the child.

Gordon (32) remarks: "In a study of a large number of diabetic mothers, it is noted that the diabetic condition is improved from the second to the seventh month of gestation. Increased carbohydrate demand of gestation requires more insulin than the mother can supply. It is reasonable to

assume that the increased supply of insulin is derived from the pancreas of the fetus, or that the fetus metabolizes the surplus carbohydrate with the insulin it produces. This would account for the increased size of the pancreas in these fetuses at term."

Collens and Schack (20) found in their two cases that the tolerance progressively diminished with advancing pregnancy. They also found a short transitory improvement during the puerperium which was followed by a permanent reduction of glucose tolerance as compared to the patient's pre-pregnant status. Bowen and Heilbrun (10) found a loss of tolerance in three of their five cases.

Lawrence (42) discusses the course of a twin pregnancy in a diabetic woman as follows: "Up to the twenty-seventh week of pregnancy the mother's carbohydrate tolerance deteriorated. From the twenty-eighth week to the end of pregnancy a great improvement, to the extent of at least 100 grams of carbohydrate a day, took place. This increase in tolerance was not maintained after labor. It can therefore be ascribed only to fetal insulin aiding the diabetic woman. The mother's carbohydrate

tolerance was slightly greater after than before pregnancy." Gray and Feemster (34) are of the opinion that the diabetic condition is definitely improved during the last trimester. Kramer (40) in his study of a group of 665 diabetics found 149 or 22.4 per cent of the cases improved, 124 or 18.6 per cent of the cases worse, 166 (25 per cent) the same, and 226 (34 per cent) not mentioned.

At the present it would be impossible to say definitely whether pregnancy improved, has no effect, or makes the diabetes worse. It seems to the writer that the important thing to glean from the whole problem is the fact that in a goodly number of the cases there is a definite hypertrophy and hyperplasia of the islet cells of Langerhans in the fetus. Further that this hypertrophy is no doubt due to the hyperglycemic state of the maternal blood. Therefore, if we during the course of gestation in a diabetic woman, by careful and adequate control of her disease, avoid throughout the pregnancy a high or increased blood sugar, we will thereby remove the stimulus to the fetal pancreas responsible for the changes seen so often in the islet cells.

(24). By doing this we attain two goals: (1)

The incidence of hypoglycemic shock in babies born of diabetic women will be reduced; and (2) By adequately controlling the diabetes the mortality and morbidity of the pregnant diabetic will be improved.

The successfulness of the treatment of the pregnant diabetic depends upon skillful unwavering thoroughness on the part of the physician coupled with intelligent co-operation on the part of the patient. As pointed out by most writers (24, 77, 40 and others) the carbohydrate intake should be high and the insulin adequate to control the diabetes. The patient must be seen at regular intervals and records of blood sugar and urine sugar kept in order that her status may be followed continuously, thus making possible an early change of tactics when indicated.

The method of delivery depends to a large extent upon the attending man's judgment. If there is any indication that the labor will be prolonged and difficult, a Caesarian section should be performed. Otherwise it is best to allow the patient to deliver by the natural route. Again as pointed out under the discussion of surgical complications ether and chloroform anesthesia are contraindicated,

and the anesthetics of choice are the same as listed there. (41, 42, 77, and others.)

S U M M A R Y

Before 1922 the diabetic woman because of amenorrhea, the failure to ovulate, cervicitis, vaginitis, vulvitis, and the shortness of her life rarely became pregnant. When and if she did, it is doubtful that she ever survived pregnancy. However, with the control of diabetes, by the use of insulin, the diabetic woman now lives longer and sterility is becoming less common because of the relatively infrequent occurrence of menstrual disorders in the controlled case, thus the incidence of pregnancy and diabetes is definitely on the increase. However, it is still quite rare. One author states that the incidence is about one in one hundred thousand pregnancies.

The prognostic outlook from both the maternal and fetal side though decidedly better than during the pre-insulin days, is still not too hopeful. The chances the mother has of giving birth to a live and healthy child are much less than those of the non-diabetic. Miscarriages, stillbirths, and abortions occur in about thirty per cent of the

cases. Death of the fetus following delivery from hypoglycemic shock or some other disturbance is by no means rare. Further the child born of a diabetic mother stands a very good chance of becoming a diabetic during his lifetime. The diabetic woman when she becomes pregnant is taking a responsibility that may end in disaster not only for the child but also for herself. Coma, hydramnions, toxemia, infections, and large babies with difficult labors are decidedly more common than in the non-diabetic. Her liability as stated by one author is ten times that of the non-diabetic.

The hyperglycemic state of the maternal blood with inadequate quantitative or qualitative insulin affords a stimulus to the pancreas of the developing baby. This results in increased development of the island cells of the pancreas of the baby. These islands are increased in number of cells, size of cells, and number and size of islands. Such a pancreas is hyperactive and is responsible for the hypoglycemic reactions occurring shortly after delivery. This pancreas is also responsible for the improved state seen in a large percentage of pregnant diabetics. It does not occur in all cases

and because it is not fully understood has led to many conflicting opinions occurring in the literature. In some cases the diabetes is improved, in others it is made worse, while in still others there is no apparent change. From the literature I am of the opinion that the group composed of those who show improvement or no change is decidedly greater than the group which is made worse.

By controlling the diabetes during pregnancy thus keeping the blood-sugar within normal limits it may be possible, by thus removing the stimulus, to prevent the development of such a hyperactive pancreas in the baby. Such control of the diabetic state will also definitely improve the maternal prognosis.

The treatment of the pregnant diabetic requires frequent and careful observation of each individual case during and throughout the whole pregnancy and puerperium. A high carbohydrate intake with adequate insulin is required. The diabetic state must be controlled throughout the whole period of gestation. Delivery should be by the natural route unless there is a suggestion that there may be difficulty. Under the latter circumstances

Caesarian section is advisable. Chloroform and ether are again contraindicated. The anesthetics of choice are the same as those already mentioned in the discussion on surgery.

Lactation tends to reduce the glucose concentration of the blood. The diabetic mother should not further burden her system by nursing her child.

C O N C L U S I O N S

A. INFECTIONS

1. Insulin has increased the diabetic's life span.
2. Infection, regardless of its severity, may precipitate diabetes, does frequently make the diabetic state worse, and through acidosis and coma may terminate it.
3. Infection decreases glucose tolerance and decreases quantitatively and/or qualitatively the effectiveness of both the endogenous and the exogenous insulin in both the diabetic and the non-diabetic. The effect is most marked in the former.
4. The loss of tolerance in the face of infection is due possibly to a combination of factors: (1) Toxins, (2) Fever, (3) Increased activity of thyroid and adrenals (antagonists to islet cells), and (4) Possibly an enzyme destroying insulin.
5. With infection degenerative changes occur in the cells of the pancreas and liver as well as in other tissues.
6. Bacteria grow more rapidly in hyperglycemic blood.

7. The diabetic's natural and acquired immunity is decreased.
8. In treating the diabetic with infection, eradicate the focus of infection as soon as possible, use a high carbohydrate diet or glucose by vein if necessary with enough insulin to control glycosuria and keep blood-sugars normal, force fluids, and give alkalies. The removal of the focus of infection leads to rapid recovery of tolerance.
9. Diabetic coma can simulate an acute abdomen.
10. It is better to prevent than to cure infection in the diabetic.

B. SURGERY

1. Surgery as a complicating factor is becoming more common and of major importance.
2. Insulin has improved the prognosis of the surgical diabetic.
3. No diabetic should be denied elective surgery. The mortality here should not be greater than in the non-diabetic.
4. Emergency surgery for removal of foci of infection is most effective when done as early as possible.
5. The success of the surgical procedure depends

to a large extent upon the peroperative, operative, and postoperative care.

6. Preoperatively the patient should receive a high carbohydrate diet or glucose intravenously with sufficient insulin to preferably keep the urine with a slight trace of sugar and the blood-sugar slightly above normal.
7. Operatively the patient should have a competent anesthetist and should never receive chloroform or ether. Anesthetics of choice are: (1) Spinal or local, (2) Gas, (3) Avertin, and (4) Gas ether.
8. Postoperatively the patient should receive a high carbohydrate diet or glucose intravenously with adequate insulin to keep the urine sugar free and the blood-sugar normal or slightly below normal.
9. Acidosis and coma are combated by high carbohydrate intake or intravenous glucose with adequate insulin, forcing fluids, and alkalies.
10. Wounds heal most readily and infection is less common if blood-sugar is normal or slightly below normal.
11. The diffuse arteriosclerosis is indeed the great-

est hazard of the surgical diabetic and still beyond our scope.

C. PREGNANCY

1. The use of insulin, by controlling diabetes has improved the menstrual cycle and ovulation of diabetic women, increased their life span, and improved their health to such an extent that pregnancy in diabetes is definitely on the increase.
2. Diabetic mothers are decidedly more liable to develop acidosis, coma, toxemia, infection, and are apt to have long difficult labors.
3. The hyperglycemic state of the maternal blood stimulates the fetal pancreas with a subsequent hyperactive fetal pancreas, which may improve the maternal diabetes during the period of gestation.
4. Hypoglycemic shock in babies of diabetic mothers occurs commonly and shortly after delivery.
5. Diabetic mothers give birth to relatively large babies.
6. Diabetic mothers in about thirty per cent of the cases either do not go to term or give birth to dead babies.
7. The liability of the diabetic mother as stated

by one author is ten times that of the non-diabetic.

8. High carbohydrate intake with adequate insulin and control of the diabetic state throughout the period of gestation may prevent the development of a hyperactive fetal pancreas, and does improve the maternal prognosis.
9. Delivery should be by the natural route if possible. Caesarian section is indicated with suggestion of prolonged or difficult labor.
10. Anesthetics used should be the same as those used in surgery.
11. Nursing is contraindicated in the diabetic mother.
12. Children born of diabetic mothers stand a very good chance of developing diabetes.

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