DIABETES

The following abstracts conclude the proceedings of the Diabetes course presented by the Frank E. Bunts Educational Institute on March 17, 1949. The first portion of these proceedings appeared in the July issue of the Cleveland Clinic Quarterly.

HYPERINSULINISM

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Rational management of the many causes of hypoglycemia must be directed at the surgical removal of the cause, or the employment of medical measures designed to control the occurrence of low blood sugars. Surgery is indicated in only a small percentage. Among the larger medical group, dietary management highly successful in controlling one type, may at times intensify the hypoglycemia in others. Differential diagnosis at times may depend upon such a therapeutic test. Approximately 80 per cent of all cases are of functional origin. The hypoglycemia attending Addison's disease, Simmond's disease, severe renal glycosuria, lactation, Von Gierke's disease, severe inanition, or following gastric resection are usually quite easily recognized. Liver disease does not usually produce significant hypoglycemia until advanced hepatic insufficiency has occurred. By this time such patients are generally gravely ill and show other clinical signs of liver disease. Hypoglycemia associated with pituitary failure is less readily separated, but here there may be x-ray evidence of destruction of the clinoid processes, visual field changes, low urinary excretion of follicle-stimulating hormone and 17-ketosteroids, as well as clinical evidence of hypogonadism.

In hyperinsulinism due to islet cell adenoma, islet cell hyperplasia, or islet cell carcinoma, the patient usually has some type of spell or attack. Usually, each attack follows the same general pattern as characterized the preceding one. The intensity of the attack tends to vary from time to time, but usually increases in both frequency and severity with time. They appear characteristically during sleep or in the early morning hours prior to breakfast. They are commonly precipitated by fasting, delayed meals or by exercise. The symptoms are promptly relieved by food. The increased food consumption either to prevent the attack or to allay hunger commonly leads to weight gain. Obesity may actually become so extreme as to introduce an added operative risk and increase the technical problem of the surgeon. The symptoms attending the attacks may be of a wide variety, but are usually of a similar type in the same individual. The symptoms in general behave similarly to those attending insulin shock in diabetic patients. They may include nausea, sweating, pallor, syncope, restlessness, muscular spasm or convulsions, apprehension, confusion, disorientation, mania or coma. The same attempts at dietary manipulation so uniformly successful in the control of functional hypoglycemia do not ordinarily modify the clinical features in this type of case. Blood sugar determinations are invariably below 50 mg. per cent fasting even in the absence of symptoms.

In contrast the fasting blood sugar level in functional hypoglycemia is normal and is not abnormally depressed by prolonged fasting. Hypoglycemic symptoms are usually mild and characteristically appear two to four hours after eating. The patient is less likely to be aware of the relationship between symptoms and the relief obtained from eating. Chronic fatigue, headache, or loss of appetite may be the only indication of ill health. Measures designed to prevent the normal postprandial rise in blood sugar, such as a low carbohydrate high protein diet with feedings between meals, invariably abolish the symptoms and the hypoglycemia.

Even in the best of hands, surgical failures are apt to occur when the diagnosis is correct. In Whipple's own series, 8 patients required a second operation to eliminate

the functioning adenoma. There are a number of reasons for surgical failure to correct hyperinsulinism. First, the tumor may be overlooked the first time. If it is in the body or tail of the pancreas, its favorite site, it can usually be seen or palpated with ease. Such tumors have a definite feel, are usually about the size of a marble, and can be palpated with the fingers and thumb, but when the lesion is located in the head of the pancreas the duodenum must be mobilized in order to identify its location. On rare occasions islet cell tissue may have an aberrant location.

Occasionally the removal of a pancreatic adenoma fails to induce a cure. This may be for a number of reasons. There may be another adenoma, since 15 per cent occur in multiple locations. A small percentage of patients having adenomas also have diffuse hyperplasia of all other islet cell tissue. Partial or total pancreatectomy has been done in many of these, but generally the end result is quite disappointing. In the remaining failures carcinoma with distant metastasis may be present. Among 149 cases of islet cell tumors known to cause hypoglycemia, 15 were accompanied by distant metastases.

Three principal reasons for advocating surgical exploration when the symptom complex described by Whipple is presented are outstanding. Permanent damage to cortical cells from repeated attacks of hypoglycemia has been observed. A few patients have had to be committed. Extreme obesity may appear to complicate the problem further when surgery ultimately is undertaken. It is often difficult to determine whether the lesion is benign or malignant even after adequate histologic study. It is well to remember that records in proved cases show 1 in 10 to have distant metastases.

DIABETES IN CHILDREN

*Henry J. John, M.D.**

There are about 120,000 children in the United States under 20 years of age who have diabetes. In my series of 6000 cases of diabetes, there were 500 in children. Of these 6000 diabetic patients 4.5 per cent of the total were in the first and 4.2 per cent in the second decade. The sexes were equally represented, 51 per cent in boys and 49 per cent in girls. An hereditary factor in the diabetic children was found in 31.5 per cent. Infection as a predisposing factor was present in 122 cases, the diabetes following the infection in from a few days to two months. Over a period of twenty-seven years 61 children, or 16.7 per cent of the total, have died; 83.3 per cent are still living. Coma has been the greatest cause of mortality which has accounted for 24 deaths over a period of twenty-seven years. In the cases of coma which I have personally cared for, the mortality rate has been 3.7 per cent. Abuminuria has appeared in 31.3 per cent of the children. Deaths from intercapillary glomerulosclerosis occurred in 11 children, accounting for 18 per cent of the total mortality.

The progress of children with diabetes is invariably good for the first two or three years. After that time complicating factors frequently enter into the situation such as breaking the diet or infections. As years go by, therefore, the diabetic child requires more and more insulin. This is largely due to the increase in weight in the child which requires increase in the calorie intake and, of course, additional insulin. Also, failure to stick by the diet and infections are likely to cause a need for increased insulin. Even children who have been carefully controlled by diet and were remaining on such a diet showed a need for increased insulin as the years passed. After ten, fifteen, or more years signs of arteriosclerosis, retinal hemorrhage, and albuminuria began to appear in about one-third of the children who were by this time adults.

Camps for diabetic children are helpful and greatly needed. Most of the children show considerable improvement during a properly supervised camping period. Their morale is improved, and the most encouraging feature is the complete transformation

of the few introspective, depressed children who begin to realize that there is much fun in life.

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DIABETES AND PREGNANCY

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The problem of diabetes and pregnancy has become more important with the steady increase in the number of potential diabetic mothers. This increase is the result of improvement in overall treatment. Today, one out of every 300 to 500 pregnancies is complicated by diabetes. Pregnancy often brings out "latent" diabetes as indicated by the observation of one-fourth to one-half of this special group in whom diabetes was first discovered during the course of pregnancy. The mere presence of reducing substance in the urine in pregnancy cannot alone, however, be taken as indicative of diabetes, until lactosuria and renal glycosuria have been ruled out. The glucose tolerance test, especially the intravenous type, is essential for accurate diagnosis.

Certain normal physiologic changes of pregnancy, such as the elevation of metabolism rate, increased pituitary activity, lowering of serum base and the greater tendency to ketosis, all combine to alter the diabetic status and make treatment more difficult. Vomiting during pregnancy and the muscular effort of labor may complicate diabetic regulation. The role of the fetus in producing insulin has been overestimated if one can judge from actual insulin requirements during the course of pregnancy. In 70 cases reported by White, only 10 needed less insulin, 14 did not change, while in 46 (or 2/3) the amount of insulin used in the last trimester represented an increase.

With good care pregnancy in the diabetic mother does not present a hazard to life today. However, toxemia occurs in 20 to 40 per cent of this group, as compared to 5 to 10 per cent in non-diabetic mothers, and polyhydramnios develops in 10 per cent, a much higher proportion than in the non-diabetic group. The danger of pregnancy chiefly concerns the fetus. Before insulin, fetal mortality was greater than 50 per cent and in many clinics today in the insulin era, the mortality is still 25 to 30 per cent. Special care, however, has been a potent factor in reducing the figures to 10 to 15 per cent. Babies from diabetic pregnancies tend to be larger than normal. Major congenital malformations are found in 2 to 3 per cent and neonatal complications, such as anoxia and cyanosis, occur more frequently. Fetal hypoglycemia is found perhaps a little more often, but seldom can be held responsible for clinical symptoms and is easily avoided by giving intravenous glucose during delivery.

The management of diabetes and pregnancy is somewhat complicated and requires the closest cooperation and supervision of the internist, obstetrician and pediatrician to bring about a successful outcome. A high protein, low salt diet seems to minimize and mitigate the occurrence of toxemia. Carbohydrate intake should exceed usually 175 or 200 Gm., but calories should be adjusted carefully so as to avoid obesity. Because fluctuations in insulin requirements and lability of blood sugar frequently occur in these cases, regular insulin has been the insulin of choice with protamine dosage adjusted downwards to avoid nocturnal hypoglycemia. Pregnancy is usually terminated at thirty-six to thirty-eight weeks, the exact time depending on the size of the fetus and presence or absence of complications, such as toxemia and hydramnios. The obstetrician should decide whether medical induction or caesarean section should be used for delivery, although the latter is looked upon with growing favor because of lessened danger to the fetus. Anesthesia should be minimal and least calculated to upset mother and fetus. Spinal anesthesia has proven of value.

Intravenous glucose during delivery will insure a normal or high blood sugar in the

baby at birth, but blood sugars at four to eight hour intervals for the first twenty-four hours can be obtained as a further check. Glucose may be given to the baby if the blood sugar falls below 40 mg. per cent and at the same time is associated with clinical symptoms. The baby should be treated as premature in most cases, and incubator and oxygen therapy used as indicated.

The status of hormone therapy as advocated by White and her associates is still a controversial one. The cost of hormone therapy and the difficulty in obtaining adequate hormonal assays make routine use of hormones impractical for the majority of diabetic pregnancies. Many observers believe that the favorable results obtained by Dr. White can be ascribed to meticulous medical, obstetric and pediatric care, since similar results are now being obtained at other clinics which provide a similar type of treatment without the addition of hormones.

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DIABETIC RETINITIS

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The etiology of diabetic retinitis is not well defined. As to whether glycosuria is of any significance is of doubt. Hyperglycemia is probably not the entire picture as many patients do not develop retinal changes for many years. Lipoid metabolism may be a factor. Hypertension and arteriosclerosis may play a part. There is no one known toxic or metabolic substance which causes the retinal changes in diabetes; uncontrolled diabetes is the only known factor. Elwyn feels that the hemorrhages must be considered the result of the dilation of the terminal vessel units and the hyaline and lipoid deposits in the retina in diabetes is the result of subnutrition and suboxidation in consequence of the persistent dilatation of the terminal vessels. He feels that the persistent dilatation of the pre-arterioles, capillaries, and post-capillary vessels in the retina is the immediate cause of the retinal changes in diabetes. The exact cause of this dilatation of the terminal vascular elements in the retina is not clear although it may be related to a persistent hyperglycemia.

The findings in diabetic retinitis are usually bilateral. In a series of 47 cases we found 4 of the patients to have bilateral retinal changes and only 2 to have unilateral changes. The changes primarily involve the posterior pole of the eye, being most commonly located between the superior and inferior temporal vessels. The disk is usually normal, and edema is not considered to be a constant finding in diabetes.

A severe complication is proliferating retinitis, which may occur without extensive hemorrhage into the vitreous but often follows a pre-retinal hemorrhage. Fortunately, this is a relatively rare complication. However, in our small series of cases, we have seen retinitis proliferans in 8 patients. In these cases, there is a primary formation of new blood vessels with secondary production of connective tissue.

Another complication is a rupture of a pre-retinal hemorrhage into the vitreous, causing a sudden loss of sight. This can usually be recognized by the fact that the patient states that his vision has been lost suddenly, and upon examination one finds that the fundus reflex is black.

The treatment of diabetic retinitis is unsatisfactory. Local treatment is of no value. The use of the eyes should not be too restricted. The use of rutin, vitamin C, vitamin P, etc. has not proved of value in influencing the retinal hemorrhages. The primary and basic treatment is that of the diabetes itself. The maintenance of a normal blood sugar does not mean that the hemorrhages will disappear as often they remain for many months after adequate blood levels are established. Nevertheless, an effort should be

made to establish a normal blood level until a better method of treatment is determined. One must always be on the alert for any glaucomatous changes.

The prognosis is not too hopeful since sooner or later nearly all cases of diabetes develop retinal changes, although the prognosis as to life is good. These changes must be accepted as a component part of diabetes and not as a complication.

NEUROLOGIC PHASES OF DIABETES

Louis J. Karnosh, M.D.

All physical disorders, if they are to have a practical and sensible classification should be presented from the standpoint of etiology and treatment. This applies particularly to the somewhat baffling neurologic entities associated with diabetes. Heretofore, any pain or discomfort occurring in a patient with diabetes has invariably been labelled "diabetic neuritis." Practically every kind of peripheral pain or paresthesia experienced by a diabetic patient has been given such an appellation.

"Neuritis" is a misnomer if for no other reason than that it implies an inflammation of a nerve which in diabetes is exceedingly rare, for diabetes is not an infectious disease.

If it is kept in mind that diabetes imposes two primary changes upon nerve tissue, a classification of diabetic neurologic disorders will not be too much of an anatomic nightmare. Being essentially a deficiency disease, diabetes produces a degeneration of the myelin sheath, i.e. the insulating material of the nerve fiber suffers chemical disintegration. The demyelinization which first occurs is usually in the most distal nerve fibers but can be found anywhere along the course of a nerve trunk, and even in the region of the posterior roots. The same process, in severe and neglected cases, may ascend into the spinal cord, along the posterior column and up into the white matter of the brain. Hence, almost any kind of neurologic symptom, both peripheral and central can occur in diabetes as it does in all deficiency diseases, and it may be anything from a mere tingling or burning of the toes to a true organic dementia.

The second major type of neurologic defeat in diabetes is one which develops secondarily to vascular disease to which almost all diabetic patients, particularly in the older age ranges, are susceptible. Such neurologic disorders are considered to be due to ischemic changes in the nerve tissue. Again such changes may occur in the very distal portions of the nervous system or may develop in the cord and brain substance. In certain instances degenerations secondary to vascular disease can be observed directly with the ophthalmoscope in the fundi of the chronic diabetic patient.

Accordingly, any feasible classification of diabetic neurologic disorders should be based upon this recognition of the two modes of disease production, namely the direct action on the myelin sheath and the effect upon nerve tissue produced by ischemia.

Because the most distal nerves are primarily affected by myelin sheath degeneration and because the most peripheral vessels are usually the first to suffer arterial degeneration, diabetic nerve disorders have a striking predilection for the lower extremities and by far most of the aches, pains, and paresthesias of the diabetic patient are referred to the thighs, legs, and feet.

A. PRIMARY DIABETIC NEUROPATHIES

First to be considered are the disorders which can be assigned to primary degeneration of the myelin sheath. In this group it is assumed that the diabetic person is younger and that evidences of considerable arteriolar or peripheral vascular disease are not striking or are completely lacking.

1. Primary Diabetic Acroneuropathy. This disturbance is identical with the neuropathy of any deficiency disease such as pernicious anemia, beriberi and the early stages of so-called alcoholic polyneuritis. In diabetes it is almost entirely restricted to the feet,

which are the site of numbness, tingling paresthesias, burning sensations of the soles and of the dorsum of the feet. The disorder is always symmetrical and is likely to be most bothersome at night when the feet are under the covers. The patient finds some relief in rubbing the parts and expresses the idea that the circulation is poor.

Circulation, however, is adequate and objective vasomotor changes are not demonstrable. Neurologic findings are present but are usually overlooked. Early absence or diminution of the ankle jerks is the rule. Sensory defects do occur but are evasive. They consist of a blunting of the finer discriminative or gnostic sensations, such as appreciation of two points, of accurate localization and of position sense in the toes. Pain sensation, however, is actually exaggerated and the pin prick induces a rather diffuse and disagreeable experience over the sole even after the stimulush as been removed.

II. **Diabetic Radiculopathy.** This disturbance is the one which produces the most common and most severe forms of what the clinician calls "diabetic neuritis." The onset is relatively acute, and it may occur in the young person, in whom vascular disease is not suspected, as well as in the older diabetic patient. At the height of the process the degree of discomfort and disability is frequently severe. The pain is sharp, often excruciating, and is usually referred along the obturator, the femoral and less commonly the sciatic nerve. It is typical root pain. As in all neuralgic pains there is a paucity of objective sensory or reflex changes and frequently the patient is regarded as being neurotic. Proof that the condition is a true root disease is found in the fact that a large majority of these patients have an elevated protein in the spinal fluid and in every sense the condition simulates a tabetic root crisis.

III. **Diabetic Pseudo-tabes.** Diabetic patients in whom demyelinization of the sensory roots of the spinal cord causes neuritic pain, if neglected may develop an ascending degeneration of the posterior column of the spinal cord. This process is a familiar picture to the pathologist and the degeneration is almost identical with that seen in pernicious anemia. Such a patient develops ataxia, loss of tendon reflexes in the legs, loss of position sense, muscular hypotonia and flabbiness and even trophic ulcers. To complete the picture the pupils may become sluggish to light or even fixed, so that only a serologic test of blood and spinal fluid may be necessary to differentiate the condition from a true tabes dorsalis.

Treatment of these three neural degenerations is of prime importance because early and adequate care of diabetic acroneuropathy and of diabetic rediculopathy may prevent the third disorder, diabetic pseudo-tabes. The first two can be corrected but once the third process develops the outlook is decidedly poor.

If myelin sheath degeneration occurs in the peripheral nerves or even in the dorsal roots, the process can be reversed with usual diabetic control and with whatever supportive measures seem to be indicated.

Lewy (J. Nerv. and Ment. Dis. 89:1, 1939.) has emphasized the three vital measures in treating myelin sheath degeneration in polyneuropathy and root neuralgia. They are as follows: (A) Increase, not decrease the sugar intake, (B) Add enough insulin to utilize the additional carbohydrate, (C) Supplement every increase in carbohydrate with a parallel increase in Vitamin B. This means not only a liberal oral dose of all vitamin principles but daily intravenous administration of nicotinamide, 100 mg. and thiamine chloride, 40 to 50 mg. for a period of six to eight weeks. This program is particularly necessary in the management of a stubborn diabetic root pain, and the improvement can often be measured in this instance by the gradual reduction of spinal fluid protein to normal levels.

Analgesics for symptomatic relief of diabetic paresthesia or pain is an important item. Such drugs should always be used sparingly, for their use may mask the value of

the basic treatment. A favorite drug has been codeine which is often given in fairly high doses. Apart from its unfavorable side actions, it is prone to lead to habit formation and may be demanded long after genuine root pain has disappeared. Demoral is even worse and should be definitely avoided. The patient may justify its use on the claim that its withdrawal may cause a relapse of the neuralgic discomfort and at best it is difficult to deprive a patient of the general sense of well-being which the drug produces. Aspirin is safer because its action does not include a relief of psychoneurotic tension as do the true narcotics.

Since all neuropathies are regarded as disruptions of enzyme systems in the neurone, the use of a dithiol, particularly British Anti-Lewisite (BAL), should be considered in treating severe diabetic and other metabolic peripheral nerve diseases. (Furmanski, A. R.: Arch. Neurol. and Psychiat. 60:270, 1948). Inasmuch as the metabolism of carbohydrate in diabetes involves essential enzyme systems the use of BAL in diabetic neuropathy should be undertaken with caution.

It should be pointed out that even if the clinician succeeds in aborting the myelin degeneration in diabetes, there is a constant tendency to recurrence in a certain type of patient. Why this susceptibility should exist in one case and not in another is still an unanswered question. The degree of neuropathy is never parallel to the degree of diabetes. A patient with mild diabetes may develop a rapid and malignant degeneration of peripheral nerves and spinal cord while many older and pronounced diabetic patients may be utterly free of all neurologic symptoms.

The integrity of the liver, the hydrochloric acid of the gastric juice, phosphorus and sulphur metabolism and even the emotional state have all been implicated in this problem.

B. DIABETIC—VASCULAR DISORDERS

The second major group of neurologic disorders in diabetes are those due to vascular disease. Here, the nerve tissue suffers as a result of ischemia and the problem of the moment is the degeneration of the arterial wall and the development of obliterating arteriosclerosis which occurs not only in the peripheral tree but also in the blood vessels which nourish the spinal cord, the brain stem and the cerebrum.

1. **Ischemic Neuropathy.** This process produces pain by implicating the fine arterioles which nourish the nerve trunks themselves, namely the vasa nervosum. The whole subject of nerve trunk ischemia has been pursued with extensive investigations by Denny-Brown and Brenner. (Arch. Neurol. and Psychiat. 51:1, 1944), by Roberts (Am. Heart J., 35:369, 1948) and Porter and Wharton (J. Neurophysiol. 12:109, 1949). Early degeneration of the vasa nervosum causes ischemia of the nerve trunk which is invariably announced by deep pain. This occurs long before other tissues show objective evidence of vascular disease.

Ischemic neuropathy in diabetes has an insidious onset and is usually found in patients over 40 years of age. The incidence is twice as great in men as in women. Its symptoms are almost identical with those in the early stages of Buerger's Disease, and they consist of pain in the deep muscles of the thighs and legs, paresthesias of the feet and toes, and cramps, especially at night. Pressure over the calves and particularly along the course of the main nerve trunks elicits tenderness and exaggerated pain. The tendon reflexes gradually disappear. The trouble is always in the lower extremities with greater involvement being most distal where earliest evidences of obliterating vascular disease are detected.

The course is gradually progressive and discomfort increases in direct proportion to the advance of obliterating arterial disease. With the appearance of unmistakable circulatory defect, the pain becomes an intolerable ordeal which makes walking or

standing impossible. Occasionally considerable improvement after many months may occur if the vascular status of the limb improves.

Naturally, the only treatment of value is that which is directed toward improving peripheral circulation. Tobacco should be prohibited. Promoting vasodilatation by drugs, the use of mechanical devices such as the Hermann pump, rest in bed, the administration of analgesics and various surgical procedures utilized by the vascular surgeon are the measures indicated for treatment of ischemic neuropathy.

II. **Diabetic Ischemic Disease of the Central Nervous System.** Even though vascular disease may not exist in the brain of a diabetic patient, pathologic changes do occur in the cerebral tissues in the form of patchy degeneration or demyelinization. This is particularly true after several bouts of diabetic coma. Nonetheless such changes rarely produce mental or neurologic symptoms and in a relatively young diabetic person in the pre-arteriosclerotic years, the clinician rarely encounters symptoms or signs which can be rightfully called diabetic encephalopathy. Therefore, until vascular disease actually intervenes, it is doubtful whether diabetes causes any serious disturbance in cerebral function. Psychosis due to diabetes is usually a psychosis based on some irregularity in cerebral blood supply, and it is therefore natural to find that most disorders of the central nervous system in diabetes are assumed to be an expression of cerebral vascular disease.

By far the most frequent lesion of the brain in diabetes is cerebral thrombosis. This may occur in the self-same arteries which are susceptible to apoplexy in the aging individual with cerebral arteriosclerosis and without diabetes. There may be a preference for certain arteries in diabetic cerebral arteriosclerosis, but we cannot be sure. Perhaps the posterior-inferior cerebellar artery can be designated as the artery of diabetic thrombosis for fully 50 per cent of cases of thrombosis of this artery which produces the so-called syndrome of Wallenberg are found to be diabetics. Otherwise the arteriosclerosis of diabetes in every respect is the arteriosclerosis of old age with its predilection for the perforating arterioles arising from the middle cerebral artery and ending in the substance of the internal capsule.

Again, it must be pointed out that there is no direct parallel between the degree of diabetes and the degree of cerebrovascular disease. By and large the worst form of arteriosclerosis occurs in the mildest cases of diabetes and one is forced to the disturbing conclusion that the diabetes itself fails to provide a completely satisfactory explanation for the early incidence of cerebral vascular accident in the victim of that disease.

Frequently it is next to impossible to establish a metabolic balance in this type of patient because the sugar regulating mechanisms in the hypothalamus may be involved in the degenerative brain disease. Circulatory stimulants may be useful such as caffeine, coramine, and possibly nicotinamide. The anticoagulant principles, heparin and dicumarol, usually are not employed because of the difficulty in making a positive diagnosis of thrombosis as against hemorrhage.

There remain large gaps in the knowledge of why some diabetic patients develop degeneration of the myelin sheath, and why others suffer with premature arterial disease. The evidence seems to indicate that some etiologic factor or group of factors other than an elevated blood sugar or glycosuria are responsible but so far have kept their identity well concealed.

THE KIDNEY IN DIABETES

Robert D. Taylor, M.D.

The vascular lesion of diabetes which appears in the kidney was well named intercapillary glomerulosclerosis by Kimmelstiel and Wilson. They described a syndrome, which now bears their names, that accompanies this process. It consists of diabetes,

proteinuria, arterial hypertension, and dependent edema. The histopathologic abnormality is made up of widespread deposits of hyaline material between the capillaries of the glomerular tuft. Laboratory tests show depression of filtration rate which is greater in degree than the damage to tubular function. Proteinuria amounts to 2 to 5 Gm. per twenty-four hours and is accompanied by pyuria (1,000,000 to 10,000,000 white blood cells per twelve hours, Addis count) and cylindruria (100,000 to 500,000 per twelve hours) with little, if any, hematuria.

This process must be differentiated from chronic glomerulonephritis. Intercapillary glomerulosclerosis is always accompanied by diabetes which is usually long existent and often has been improperly treated. The degree of anemia in the renal disease of diabetes is usually less striking than in glomerulonephritis. Hematuria of more than 1.0 million cells per twelve hours is unusual while this is a diagnostic feature of glomerulonephritis. The rate of renal deterioration is customarily not as rapid among those patients with diabetes.

Management of this aspect of diabetes includes continued regulation of carbohydrate metabolism with diet and insulin. Because of the disproportionate damage between the glomeruli and tubules, glycosuria is not a reliable guide to insulin requirements. Hence, blood sugar levels must be estimated frequently. When edema is present, rigid restriction of dietary sodium to less than 1.0 Gm. per day is necessary. Ammonium chloride 1.0 Gm. four times daily is often helpful, and in some cases intramuscular injection of mercurial diuretics must be used. The last can be given as often as necessary with little fear of permanent renal damage.

If hypertension with headache is distressing, thiocyanate is helpful. This drug must be given with extreme care because the impaired renal function predisposes to toxic blood levels. It can be prescribed in the form of an elixir with equal volumes of elixir of phenobarbital. A teaspoonful of the mixture twice daily can usually be given for five to seven days without danger. After this period, the serum concentration of thiocyanate should be measured and the dosage adjusted so that the serum level does not exceed 8 mg. per 100 cc. The lowest effective concentration which controls headache should be maintained.

When azotemia appears, a diet that contains less than 0.5 Gm. of protein per kilogram of body weight per day will lessen the intensity of uremia and modify the unpleasant symptoms which accompany it.

DERMATOLOGIC PROBLEMS ENCOUNTERED IN DIABETES MELLITUS

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From 20 to 25 per cent of patients with diabetes mellitus develop various dermatoses because of the disturbance of carbohydrate metabolism. With the possible exception of the xanthoma diabeticorum and necrobiosis lipoidica the dermatoses commonly observed in a diabetic patient are not pathognomonic of that disease.

Urbach and his associates determined the sugar content of 30 to 40 mg. of human skin and found that 68 mg. per cent was the upper limit of normal. They studied the glucose tolerance curve of the skin and found among other things that in the customary glucose tolerance test the glucose content of the skin reached its maximum level in one hour after ingestion of glucose, and dropped to normal more slowly than the blood glucose level. In diabetic patients, the skin glucose level did not reach its lowest level until four hours after eating. Furthermore, they found that in diabetic patients with skin manifestations the fasting skin sugar level averaged 82.8 mg. per cent and in diabetes without skin manifestations the fasting skin sugar level averaged 65.5 mg. per cent. In diabetes mellitus, the ratio between fasting skin sugar and blood sugar is increased.

The prolonged and increased storage of sugar in the skin of diabetic patients probably explains their susceptibility to pyogenic and mycotic infections.

Generalized pruritus with or without cutaneous manifestation is often an early indication of diabetes. Dermatitis of a nonspecific type may develop on any portion of the cutaneous surface; however, in severe diabetes a moist, weeping, intertriginous dermatitis may develop with predilection for the genito-crural region, beneath breasts and in other pendulous folds. Intermittent pruritus vulvae without visible changes in the vulva may be an early manifestation of diabetes mellitus and precede for days or weeks the appearance of a vulvitis. Likewise, recurrence of acute balanitis should suggest the possibility of potential or active diabetes.

The most common dermatoses seen in diabetic patients are those caused by pyogenic and mycotic infections. Those caused by pyogenic infections are recurrent furunculosis, carbuncles, erysipelas, ecthyma, folliculitis, suppurative paronychia, hidradenitis suppurativa and other pyodermas.

The common mycotic infections which frequently cause eruptions in diabetes mellitus are usually of two types (1) those caused by monilia albicans and (2) those produced by dermatophytons. The moist, vesicular, intertriginous dermatitis involving the genito-crural region and the folds of pendulous breasts and abdomens, are apt to be caused by monilia albicans. This fungus also may cause dry or moist paronychia, onychomycosis, perleche, and erosia interdigitalis blastomycetica, which is usually confined to the webs of the second and third interdigital webs of the fingers.

Dermatophytosis may be difficult to control in the diabetic patient. Chronic dermatophytosis of the feet is occasionally complicated by recurrent acute cellulitis of the leg. Such a complication is more serious in a diabetic patient. It is also thought by some observers that neglect of dermatophytosis of the feet, or injudicious use of strong keratolytic or irritative remedies in the treatment of this dermatosis contributes to the formation of gangrene of the toes. Gangrene of the toes and feet is a well known complication of diabetes and may be hastened or precipitated by secondary infection resulting from careless cutting of toe nails, paring of corns and warts on the toes and feet of the diabetic.

Pigmentation is a cutaneous manifestation sometimes seen in the diabetic. Xanthochromia, a yellow discoloration seen chiefly in the nasolabial folds and on the palms and soles, is at times observed. The causative pigment is carotin and a lipochrome. It is thought that because of its impaired function, the liver is inhibited in its conversion of carotin of the blood to vitamin A. Hemochromatosis, or bronze diabetes, is a rare disease in which there is cirrhosis of the liver, sclerosis of the spleen and pancreas and disseminated cutaneous hyperpigmentation similar to that seen in Addison's disease. Hemochromatosis has been observed in non-diabetic patients. The pigmentation is caused by deposit of hemosiderin, melanin and hemofuscin in the skin and various organs of the body.

Dermatoses related to the disturbance of lipoid metabolism in diabetes mellitus may be divided into three types, (1) Xanthoma diabeticorum, in which the cutaneous lesions usually develop quickly and are characterized by discrete, at times grouped, small bright red globular or acuminate papules with predilection for the buttock and extensor and flexoral surfaces of the arms. Lesions may occur elsewhere. When lesions are well developed, small yellow areas of discoloration appear at their apices. The xanthomata may simulate acute papulopustules. There is an associated hyperlipemia. Xanthoma diabeticorum disappears after institution of treatment for diabetes. (2) Xanthoma tuberosum, characterized by development of pink to yellow, smooth papules and nodules with predilection for elbows, knees, palms, soles, and at times tendons is occasionally seen associated with diabetes mellitus. There is a hyperlipemia and hypercholesterolemia. The xanthoma may or may not disappear following adequate control

of the diabetes. Some observers feel that when xanthoma tuberosum associated with diabetes mellitus disappears following control of the diabetes, it should be classified as xanthoma diabeticorum; however, the clinical characteristics of the cutaneous lesions differ from those of diabetes xanthoma previously mentioned. (3) In the majority of cases of necrobiosis lipoidica which have been reported, there has been an associated diabetes mellitus. However, it has been observed in non-diabetic patients. Urbach was of the opinion that the non-diabetic patient with necrobiosis lipoidica should be considered as a potential diabetic and observed and studied with this possibility in mind. The cutaneous lesions of necrobiosis lipoidica have a predilection for the anterior and lateral surfaces of the legs. They may, however, develop on the arms and trunk. They are usually bilateral. The initial lesion is a small, flat, bright red, smooth papule. The lesion enlarges by peripheral extension to form variable sized, rounded or irregular plaques. As the lesion enlarges, its margins remain red to at times violaceous. The central portion develops a yellowish hue, with distinct atrophy of the epidermis. Telangiectases develop on the surfaces of the larger lesions. Ulceration may occur, but is not a common manifestation. Histologic changes consist of a homogenous degeneration of the collagen tissue without subsequent necrosis. At the periphery of the areas of necrobiosis, there is a mild perivascular inflammatory infiltrate, consisting of histiocytes, lymphocytes and occasional leukocytes. The vessels show varying degrees of obliterative changes. Necrobiosis does not tend to disappear with control of the associated diabetes. In some cases spontaneous improvement has been observed.

Cutaneous manifestations caused by insulin such as generalized urticaria and focal reactions at the site of injection may occur, in a diabetic patient. Focal panniculitis followed by atrophy of the subcutaneous fat, the development of lipoma-like masses at the site of repeated injections of insulin, as well as the formation of abscesses and ulcers are infrequent complications of insulin therapy.

DIAGNOSIS AND TREATMENT OF CORONARY HEART DISEASE

A. Carlton Ernstene, M.D.

Arteriosclerosis is one of the most important complications of diabetes mellitus, and because of this and the age distribution of that disease, coronary heart disease is of common occurrence in the diabetic patient. The principal clinical manifestations of coronary heart disease are angina pectoris, acute myocardial infarction, acute coronary failure, paroxysmal cardiac dyspnea, certain disturbances of heart rhythm, and congestive heart failure.

Angina pectoris is a descriptive term applied to attacks of paroxysmal pain or discomfort in the chest which are induced by exertion or emotion and are relieved promptly by rest or termination of the emotional episode. The most important measure in the treatment of the condition consists of having the patient do all that is possible to avoid the attacks. Hurry, heavy lifting, excitement and exposure to cold must be avoided as completely as possible, and all patients should be instructed to rest in a chair for thirty or forty-five minutes after each meal. Every patient should receive a thorough trial on one of the purine derivatives, such as theobromine and sodium acetate, for in a certain number these preparations result in a distinct improvement in the individual's exercise tolerance. Mild sedatives should be administered to all patients who are unduly concerned about their condition or are of an excitable nature. Every individual should be supplied with a number of nitroglycerine tablets, gr. 1/200, with instructions to use one whenever an attack is not relieved by rest within one minute.

Acute myocardial infarction is characterized, in all but a few cases, by pain similar to that of angina pectoris but generally more severe and almost always of longer duration.

Symptoms of shock of mild to severe degree appear soon after the onset in practically all patients, and fever and leukocytosis usually develop within twenty-four hours. The electrocardiogram shows diagnostic changes in practically every case if records are made every day or so and if multiple precordial leads are used in addition to the standard limb leads.

The first aim in the treatment of acute myocardial infarction is to relieve the pain. Morphine remains the most valuable drug for this purpose although papaverine hydrochloride or aminophyllin by intravenous injection gives prompt relief in certain patients. Atropine sulfate, gr. 1/150, is administered by subcutaneous injection every eight hours during the first three or four days as a possible means of preventing the occurrence of ventricular fibrillation. Severe shock may be combated by the slow intravenous administration of plasma. Oxygen is administered for the relief of prolonged pain, cyanosis or intense dyspnea. Dicumarol is given for at least three weeks provided that facilities are available for measuring the prothrombin time of the blood and provided the patient does not have renal or hepatic insufficiency or a blood dyscrasia with hemorrhagic tendencies. Digitalis is administered only to patients in whom evidence of congestive heart failure develops or in the event of auricular fibrillation with a rapid ventricular rate. The patient is kept in bed for six to eight weeks, depending on the severity of the attack, and is not allowed to resume his business or professional activities until he has been up and about for approximately the same length of time.

Certain patients who have coronary artery disease, experience attacks of substernal pain of longer duration than the pain of angina pectoris but do not subsequently present clinical or electrocardiographic evidence of myocardial infarction. The term "acute coronary failure" has been applied to this syndrome. Treatment consists of the administration of morphine or the intravenous injection of papaverine hydrochloride or aminophyllin to relieve the pain. The patient is kept in bed for ten to fourteen days rest and during this time dicumarol is administered as in the management of acute myocardial infarction.

Coronary artery disease is a common cause of acute left ventricular failure which results in paroxysmal cardiac dyspnea or cardiac asthma. The most effective measures in the treatment of an attack are assumption of the upright position and the administration of morphine sulfate or the intravenous injection of aminophyllin. All patients who have experienced a seizure should be digitalized and placed on a low sodium diet. If there have been severe or repeated paroxysms, mercurial diuretics should be administered daily or every other day until the drug no longer causes diuresis or loss of weight.

Coronary heart disease may be responsible for any one of the recognized disturbances of cardiac rhythm. It is the most common cause of auriculoventricular block which may be of any degree from simple lengthening of auriculoventricular conduction time to complete dissociation of the auricles and ventricles. The higher grades of block may be complicated by the Adams-Stokes syndrome. Adams-Stokes seizures are rare, and the actual attacks usually are of such short duration that they do not require treatment. In rare instances, however, the ventricular standstill is of such duration that life is threatened and the intracardiac injection of epinephrine hydrochloride, 0.5 to 1.0 cc. of 1:1000 solution, is indicated. The most effective drugs for preventing recurrent attacks are epinephrine hydrochloride, 0.3 to 1.0 cc. of the 1:1000 solution, subcutaneously or intramuscularly every two to four hours, ephedrine sulfate by mouth in doses of $\frac{3}{8}$ to $\frac{1}{2}$ gr. every four to six hours, and paredrine by mouth in doses of $\frac{2}{3}$ to 1 gr. three or four times a day.

Coronary artery disease often results in the gradual or rapid development of symptoms and signs of congestive heart failure. Treatment does not differ from that of myo-

cardial failure due to other types of heart disease and consists principally of absolute rest in bed, the proper administration of digitalis, sedatives, and diuretic drugs, restriction of the sodium content of the diet, and, less often, venesection and the mechanical removal of fluid from the thorax.

INDICATIONS FOR SURGERY IN DIABETIC GANGRENE

George S. Phalen, M.D.

The introduction of the sulfonamide compounds and penicillin has greatly altered the clinical course of cases of diabetic gangrene. With these drugs to combat the associated infection, the diabetes may be brought under control by medical management prior to amputation. Ten or fifteen years ago, diabetic gangrene was considered a surgical emergency; usually a high amputation was performed to get well away from the gangrenous area and to be certain of adequate circulation and healing of the stump. If the spread of infection was not promptly checked by radical amputation, the diabetes could not be controlled, and death from overwhelming sepsis was inevitable. Nowadays, with the use of antibiotics, the surgeon may not even see the patient with impending diabetic gangrene, since with proper medical treatment these cases may never need an operation. Furthermore, less radical amputations may now be performed without endangering life.

The site and type of amputation depend upon a clinical evaluation of the part. A great deal can be predicted about the viability of a member by a simple examination. Is the foot warm to touch, or does it have a perfectly cold cadaverish feel? If good sensation is present in the skin, there is usually adequate circulation beneath it. The color and elasticity of the skin also gives the surgeon a good idea about the circulation.

Palpation of the arteries in the lower extremity is also of great importance in deciding about the site and type of amputation that may be done. If both anterior and posterior tibial arteries are palpable, a local amputation of the gangrenous toe may be performed. If only the posterior tibial artery is palpable, a local amputation may still be done in many cases. If there are no pulsations palpable about the foot, but the popliteal pulse may still be felt, an amputation below the knee may be considered. If pulsation in the femoral artery is either weak or absent, amputation at a level above the knee is necessary.

If there is edema over the dorsum and sole of the foot which does not subside after a day or two of bed rest and with control of associated infection in the foot, it is likely that local amputation will not suffice. If the area of gangrene is sharply localized to one or two digits, the surgeon may be able to do a local amputation—either a simple guillotine amputation of the toe itself or a resection of the entire toe together with its metatarsal, (the "pie operation," so-called because the section of tissue removed is wedge shaped like a piece of pie). If there is severe pain in the involved foot, the surgeon may be relatively certain that a local amputation will not effect a cure.

There are many factors that affect the site of amputation. It is of primary importance to select a site that is relatively certain to heal. It is a simple matter to ascertain the adequacy of the circulation at the level of the amputation when the surgery is being performed. Since a tourniquet is not employed at the time of the operation, the surgeon has only to observe the amount of bleeding present and the viability of the tissues at the level of the amputation. If the circulation is obviously inadequate at the first level, it is certainly better to proceed immediately to a more proximal level rather than subject the patient to more than one operation. In some cases, the extent of the gangrene may not be appreciated prior to the operation. For example, a single toe may appear gangrenous and the anterior tibial vessel may have a palpable pulse; but at the time of operation

it will be seen that the ischemic necrosis involves not only the toe but also the wedge of tissue, including the toe and its metatarsal, which is supplied by the dorsal metatarsal arteries distal to the arcurate branch of the anterior tibial artery. In such a case, simple amputation of the toe will not suffice and a "pie operation" must be done.

In choosing the site of amputation, some consideration must be given to the functional value of the stump. A useful foot may remain after amputation of one or all of the toes, after a "pie operation" involving one or two rays (a toe plus its metatarsal), or after an amputation through the base of the metatarsals. Amputation farther proximal in the foot does not give a satisfactorily functioning stump. In an amputation below the knee, an attempt should be made to leave about a six-inch stump. If there is any doubt about the circulation at this level, it is usually better to go ahead with an amputation above the knee. A supracondylar amputation usually suffices, but occasionally it is necessary to amputate through the middle or upper thigh.

The age and financial status of the patient may play some part in deciding about the site of the amputation. As a rule, amputations below the knee are not satisfactory in patients past sixty years old, since the stump is almost certain to ulcerate or become painful later and re-amputation at a higher level will be necessary. In some instances, the patient may not be able to afford a prolonged period of hospitalization in the hope of saving his limb at a lower level. This patient may insist upon having an amputation at a level which will be sure to heal and enable him to leave the hospital in the shortest possible time.

If a patient already has one leg amputated above the knee, every effort should be made to salvage a stump below the knee on the other leg; or if at all possible, a local amputation should be attempted.

In performing an amputation in cases of diabetic gangrene, the guillotine type of amputation should be done if the site of amputation is adjacent to the level of demarcation. A secondary closure then may be done a few days later if circulation appears adequate in the stump, or re-amputation at a higher level may be necessary. In cases of extensive gangrene involving the entire foot where it is still felt advisable to attempt to save the patient a stump below the knee, it is much the safer procedure to do a guillotine amputation at the most distal site where circulation appears adequate. Then a secondary amputation at the site of election, six inches below the knee, may be performed within a week or ten days if there is no evidence of progressive cellulitis or gangrene.

If the site of amputation is far removed from the site of the gangrene, as a supracondylar amputation in a case of gangrene involving only the foot, then an amputation may be performed with primary closure of the stump. A soft rubber drain is always left in these stumps, however, to prevent formation of a hematoma with subsequent infection. This drain is removed in twenty-four to forty-eight hours if there is no evidence of infection or hemorrhage in the stump.

Occasionally, as in the "pie operation," small catheters may be sewed in place and the wound loosely closed. This permits irrigation of the wound with antibiotics, such as penicillin or streptomycin, to control infection and promote healing.

PRE AND POSTOPERATIVE CARE OF THE DIABETIC PATIENT

E. Perry McCullagh, M.D.

Last year in 400 new patients with diabetes the diagnosis was first arrived at in 20 on the basis of hyperglycemia in a random blood sugar test and in the absence of glycosuria in the first urine test. This was 5 per cent of all cases. In these 20 patients the diagnosis would have been missed if the blood sugar had not been estimated.

It is a matter of considerable value to the patient for his physician to know of the presence of even mild diabetes before surgery and to make suitable plans to combat it because acidosis or coma may develop if sufficient stress is imposed. Its presence, though mild, may have an important bearing on the healing of tissues or if not recognized in time postoperative complications or infections already may have established considerable acidosis before the disease is acknowledged or treatment begun. For such reasons as these we believe that all patients should have a routine blood sugar test and that it should be reported and considered before surgery is started.

The management of diabetes in the surgical patient can be considered from several angles:

(1) Differential diagnosis of symptoms due to acute abdominal conditions or acidosis;

(2) Decision as to treatment and timing of necessary operations in acidosis;

(3) The handling of diabetes in cases of elective surgery;

(4) Preoperative preparation of patients with diseases having a special relationship to diabetes;

(5) A plan for handling of diabetes on the day of surgery;

(6) Postoperative treatment and feeding of surgical patients;

(7) The diagnosis of surgical complications during acidosis or coma.

When a patient is seen in severe diabetic acidosis the diagnosis usually is readily established by the clinical appearance, vomiting, the flushing, dehydration, dyspnea, glycosuria, ketonuria and the determination of hperglycemia and a carbon dioxide combining power below 35 volumes per cent.

In all such patients various procedures are carried out as treatment is begun. These include careful consideration of signs of shock or circulatory failure, a search for infection, treatment of gastric dilatation or fecal impaction.

Under these conditions the only decision which ordinarily concerns the surgeon as well as the internist is the problem of abdominal pain and whether or not the pain may mean appendicitis which has precipitated the acidosis.

The differentiation usually can be confirmed by several means. If a good history is available it will show that appendix pain preceded coma—acidosis pain followed the symptoms of acidosis.

Acidosis pain tends to be more general than appendix pain and may involve the back and limbs or at times simulate coronary thrombosis. If fever is present, which applies to both conditions and if leukocytosis is high (and it may be over 50,000 in acidosis) these findings are of no help.

If the carbon dioxide combining power is below 35 volumes per cent surgery should not be attempted unless it is imperative. A situation seldom exists in which the patient cannot wait safely for two hours. During this time the use of adequate amounts of intravenous Ringer's solution or saline will almost entirely have eradicated the pain of acidosis while that of appendicitis remains and by that time localized tenderness may be elicited clearly and rigidity become more local.

If the carbon dioxide is 35 or above and doubt still exists, surgery is preferable to the risk of further delay.

In elective surgery the problem is entirely different. Under these circumstances diabetes should be thought of, not in terms of normal blood sugar levels alone, but in the health of the body. If the diabetes is mild and the patient in a good state of general

health, two or three days in the hospital may be well spent in obtaining good diabetic control and in becoming acquainted with insulin requirements.

In older patients, and especially malnourished ones, who come for elective surgery such as an herniorrhaphy when surgery of the skin or surgery of the extremities is involved, it is preferable to postpone surgery for one or two months. During this time not only adequate control can be established and maintained but a correct diet will have repaired many of the changes of chronic malnutrition. Strenuous weight reduction should be postponed until a later date and in the preoperative period not only are adequate calories advisable but a relatively high protein intake as well.

The procedure followed in the average case is a simple one. The full diet is maintained until the day of operation. This is important particularly in hyperthyroidism and in liver disease. On the day of operation blood and sugar determinations are done fasting. If protamine insulin is being used the dose is cut to one-half of the total as in the neighborhood of 40 units or to about ⅓ if 60 units or more have been required daily. If the operation is to be performed in the morning hours, breakfast is omitted and no regular insulin given. If the operation is scheduled for afternoon a liquid breakfast is prescribed and a third of the usual daily allowance of insulin given as regular insulin. Immediately after the operation an intravenous injection of saline or Ringer's solution of 1000 or 2000 cc. is prescribed. This contains 5 per cent glucose and to the solution is added 25 to 50 units of regular insulin for each 100 Gm. of glucose allowing the maximum in severe diabetes and the minimum in mild cases.

The blood sugar level is followed 2 or 3 times daily when the disease is severe and once daily when mild. Urine is tested on the ward for sugar every four hours and regular insulin is given every four hours, the dose varying from 2, 3 and 5 units to 5, 10 and 15 in cases of varying severity based on yellow, orange or red Benedict's tests.

As soon as possible food is given by mouth. Except where gastrointestinal surgery prevents it, clear liquids can usually be given in small amounts the first postoperative day, frequently in such a way as to make up the usual available glucose content of the diet. At first tea with sugar may be most readily accepted, gingerale may be used, and often pieces of cooked fruits may be taken without gastrointestinal disturbances. Large amounts of raw fruit juices such as orange or grapefruit juice are more likely to cause disturbances.

When caloric needs are high as in cases of liver disease, it may be advisable to continue intravenous glucose daily in repeated doses supplying a total glucose intake as high as 300 or 400 Gm. per day.

In infants or patients with bladder or prostatic surgery where urine may not be obtained readily or at frequent intervals to guide the plan of insulin doses the blood tests may be depended upon more than they would be otherwise.

Ketosis is always prevented when possible but during the first few postoperative days blood sugar levels of 150 to 250 fasting or four hours after meals may be permitted. In patients who have undergone eye surgery where the disturbance of a reaction may cause damage to the eye and in those who have coronary sclerosis low levels of blood sugar are avoided carefully.

When the patient begins to eat if vomiting seems likely and the actual food intake is not easy to predict, the insulin dose can sometimes be given more accurately by withholding the insulin until thirty to forty-five minutes after each meal.

For patients requiring clear liquids as in bowel surgery the entire glucose content may be given as tea or coffee with sugar, or as pieces of cooked fruit and gelatine mix.

tures. In many instances strained orange juice or grapefruit juice may be used and in some condensed or raw milk with no harmful effects. By the second postoperative day most surgical patients may take a liquid diet the equivalent of and supplying their usual food intake.

PERIPHERAL VASCULAR DISEASE AND DIABETES MELLITUS

Fay Le Fevre, M.D.

The only peripheral vascular disease of importance associated with diabetes mellitus is arteriosclerosis obliterans. The occurrence of arteriosclerosis obliterans is eleven times more frequent in diabetic patients than in a comparable non-diabetic group.

Early recognition is important. All diabetic persons should have a careful vascular survey and evaluation. Clinical diagnosis of arteriosclerosis is readily made. History of leg fatigue and typical intermittent claudication is common. By observing gross temperature changes, color changes, and quality of peripheral pulsations the diagnosis can usually be established. X-ray evidence of arterial calcification does not always mean that the patient is having symptomatic peripheral vascular disease.

The first principle of treatment is well controlled diabetes. There is no single approach but a combined effort using all possible methods should be made. Treatment of diabetes without clinical evidence of arteriosclerosis obliterans should consist of general foot care, foot hygiene, and fungus prophylaxis. Regular observation and checking for early evidence of vascular disease is also necessary. The diet should be low cholesterol particularly if the blood cholesterol is elevated.

The diabetic patient with early signs or symptoms should be given general foot care and Buerger-Allen exercises and careful use of heat. Contrast baths are not desirable; physical therapy consisting of whirlpool baths and pavex are useful. There is still evidence that the latter form is helpful in simple intermittent claudication on the basis of arteriosclerosis obliterans. Caudal or sympathetic lumbar blocks to determine the degree of temperature rise with thought of considering sympathectomy may be employed. Medication is of little value. Nicotinic acid, thiamin chloride, thyroid, iodides, or Priscoline can be tried. In our experience, the following are of no value: tetraethylammonium chloride, histidine and vitamin C, tissue extracts, and anticoagulants.

The diabetic patient with rest pain and/or ulceration should have: (1) immediate hospitalization; (2) the use of the oscillating bed; (3) caudal blocks for relief of pain.

Local care of ulcers includes simple saline foot soaks, alternating with 1:5000 solution of potassium permanganate. The temperature of the soaks should be between 94 and 96 F. and last twenty minutes one or two times daily. Strong antiseptic solutions and excessive moist dressings should be avoided as tissue becomes macerated. Attempts to dry up ulcer areas, promote drainage and remove crusts carefully should be made. Also sympathectomy should be considered if the response from the caudal block is good. The value of anticoagulant preparations has not been established.

In all cases: (1) tobacco should be stopped; (2) protect from cold; (3) avoid trauma; (4) use heat with great caution.

A discussion of RENAL GLYCOSURIA by A. C. Corcoran, M.D., appeared in the October, 1948 issue of the Cleveland Clinic Quarterly.

PANEL DISCUSSION (Abbreviated)

(Drs. Miller, Browne, McCullagh, Le Fevre, Schneider, and Lazarow.)

Dr. Jordan: Here is the first question. If most diseases are treated at the onset, the chances of cure are greater. Then, why should not mild diabetes be treated with insulin?

Dr. McCullagh: It is a good idea to treat early diabetes with insulin. The possibility of relieving the individual of the necessity of taking insulin later should be sufficient reason for giving insulin at the beginning and trying it at least. Children who have diabetes ordinarily have rather abrupt onsets and it is relatively severe as soon as it is found. Insulin requirements under such circumstances vary tremendously. In some of the children I have seen I have been impressed by the fact that the insulin dose, a requirement that is perhaps in the neighborhood of 50, 70, 80 units per day the first week or two or perhaps even a few days, may fall to a point where one is tempted to withdraw it completely. Ordinarily the last 5 units or 10 units cannot be withdrawn and in the same individuals it has been my experience that after another few weeks or months, the dose requirement is relatively high again.

Dr. Jordan: Another question, "Is there a reliable micro-method for determining blood sugar levels in the office?"

Dr. Lazarow: There is a micro-method that we use on our rats all the time that requires only about 1/50 of a cc. of blood. However, the reducing method used in that determination is a ferricyanide and the precipitating agent is not quite specific so that non-glucose reducing substances are also measured. Consequently, the standards used will have to be higher taking into effect the glutathione and other things which are also measured. However, a method could be adapted from the other standard methods by using some of the microtechnics which are now being developed which probably could be done readily in the doctor's office.

Dr. Jordan: Here is a question addressed to Dr. Browne. "What is the general adaptation syndrome?"

Dr. Browne: The general adaptation syndrome is a term coined by Dr. Hans Selye which describes the set of body reactions, signs, symptoms, physiologic changes, and chemical changes which occur in the body in response to damage, stress, or illness. There are a whole host of responses which occur independently of the nature of the damage or the stimulus.

Dr. Jordan: "What is the nature of the change in the glucose tolerance test caused by malnutrition?"

Dr. Lazarow: It is known that many persons placed on a starvation diet may show changes in glucose tolerance similar to what is observed in diabetes. Placing them on a high caloric diet, particularly high fat, can improve the glucose tolerance.

Dr. McCullagh: From a clinical point of view, the most starved individuals we see, the thinnest, are those with anorexia nervosa. In them two distinct types of glucose tolerance occur. In persons who have anorexia nervosa for a long time there is good evidence that they develop not only insulin failure as a result of starvation but adrenal and pituitary failure as well. This seems to me a good explanation for the flat glucose tolerance curve which one may see in cases with severe anorexia nervosa.

Dr. Schneider: Perhaps protein, as Dr. Browne has shown, is handled differently under certain circumstances and I should think it might be quite true that carbohydrate would act in the same manner.

Dr. Jordan: Does an elevated blood cholesterol have any effect on vascular changes in the diabetic?

Dr. LeFevre: I don't believe we have a specific answer to that question. The evidence in animals indicates that, particularly in rabbits, one can produce vascular

changes with a high cholesterol diet which will tend to disappear on a low cholesterol diet. We do not have such evidence for humans. What meager evidence there is, tends to point to the fact that when the blood cholesterol is elevated, say over 200 mg. per cent, keeping the cholesterol down in the diet might help to retard arteriosclerosis. There has been no good clinical work done to prove that point, but I think we might assume there is some connection, the nature of which we do not understand, between cholesterol and the production of vascular changes or the premature production of vascular changes.

Dr. Jordan: Is it generally conceded that a low fat, high carbohydrate diet produces a definite drop in the blood cholesterol?

Dr. LeFevre: In reviewing my own cases on what we call a low cholesterol diet, we haven't definitely brought down the blood cholesterol.

Dr. McCullagh: A patient we hoped to show yesterday has xanthoma tuberosum of the type often seen in diabetes. However this type of xanthoma isn't necessarily associated with diabetes. A month ago this patient had a blood cholesterol value of 428. He was put on a low fat diet and two days ago his blood cholesterol was 224. This may or may not be significant, but seems unlikely to be explained on random sampling.

Dr. Lazarow: Has there been some change in his xanthoma?

Dr. McCullagh: Very little as yet.

Dr. Miller: I would just like to put in a plea for the poor patient who is at the present time being put on various diets for the value of which we do not have good experimental evidence. The diabetic patient has enough of a problem with the restrictions that already have been imposed without adding other changes of diet which have not been proved experimentally or conclusively in the laboratory or in the clinic. The relationship of blood cholesterols and the levels of cholesterol in diet certainly is not a close one. There is no close correlation. The ingestion of 10 Gm. of cholesterol over periods of months produces little change in the blood level and for that reason until further conclusive evidence is brought forth, I would be against introducing other radical changes in the diet in these patients.

Dr. LeFevre: I should like to ask Dr. Miller how he would bring about this conclusive evidence unless these patients are put on some form of diet.

Dr. Miller: I would agree with that if this is set up on an experimental basis with adequate control and careful observation. I do not think that indiscriminate application of diet of this sort, given at random by the doctor in his office, will ever bring forth conclusive evidence. Those are strong words, but it is my opinion.

Dr. Jordan: May I ask then how many members of the panel would put their patients on a low cholesterol diet under these circumstances and how many would not?

Dr. Lazarow: Well, I have no problem because my patients are all rats. I might point out that in the laboratory it has been impossible to produce arteriosclerotic changes no matter how much cholesterol you give a rat. In a rabbit you can. The question is are we closer to a rabbit than a rat?

Dr. Jordan: We had better move on to the next question. "Should protamine-zinc insulin be used in the presence of infection?"

Dr. Schneider: That is a matter of individual preference. I think that protamine-zinc insulin can be used in the presence of infection but certainly it is not the only insulin to be used in the presence of infection. If one has previous knowledge in a given case that, let us say, the insulin requirement is 60 units of protamine per day and the individual now has an acute infection, I see no reason why that person should not continue to receive that amount of protamine insulin. We expect, of course, that he is going to require a good deal more and why not then continue the 60 units of protamine insulin

and supply additional increments of regular insulin as frequently as is indicated by the clinical requirements? That would not be advocating the use of protamine-zinc insulin alone in the management of infection.

Dr. Jordan: Is it not possible to give protamine-zinc insulin in more cases at night rather than in the morning, not overlooking its accumulative effect?

Dr. McCullagh: Yes, it is quite possible that it can be used to an advantage by giving it at night in some patients. I think it depends on what is found to suit the particular patient best, what time the insulin is given as well as what type is given. When protamine-zinc insulin was first used in Denmark, it was given at suppertime or at bedtime, but Danish dietary habits differ somewhat from ours and most of us here take a relatively small breakfast, a somewhat larger lunch, and a good deal larger meal in the evening. In general this fits in well with the gradually increasing activity of protamine-zinc insulin when it is given before breakfast.

Dr. Miller: I assume, Dr. McCullagh, you are speaking of protamine-zinc insulin alone.

Dr. McCullagh: Yes.

Dr. Miller: Mark of New York and Ricketts of Chicago have written papers in which they have demonstrated that the accumulated use of protamine given over a period of days results in a constant action on the blood sugar. Under controlled conditions, same blood sugar curves were obtained regardless of whether protamine-zinc insulin was given at breakfast, at lunch, at supper, or at night. Consequently they drew the conclusion that it was immaterial as to when the protamine-zinc insulin was given under those particular conditions. It was usually given in the morning because it was more convenient. Of course, with the use of mixtures the rate of action of the insulin is much reduced and it is quite possible under those circumstances it might be better in certain cases to give it at other times.

Dr. Jordan: Another question on protamine-zinc insulin. Why do some patients not feel well on protamine-zinc insulin?

Dr. McCullagh: Apart from local reactions or allergic reactions which some people get (it is usually quite evident when it occurs) or from hypoglycemia, I know of no reason why protamine-zinc insulin produces any particular ill feeling.

Dr. Miller: I think that the use of protamine-zinc insulin alone in the older mildly diabetic patient may occasionally give rise to untoward symptoms. This is because the disease is essentially mild with normal fasting blood sugars which rise only after meals. Protamine insulin serves merely to intensify the process lowering the blood sugar before breakfast. It is quite possible these older patients may have insulin reactions, hypoglycemic reactions, which are not manifested in the ordinary way. Of course, too, in the presence of arteriosclerosis and coronary artery disease symptoms of a reaction may be different. We have had several cases in which the use of protamine-zinc insulin not justified on the basis of blood sugar levels has resulted in rather severe clinical symptoms which have been alleviated by the actual omission of insulin. We have seldom used protamine-zinc insulin in the older patient whose fasting blood sugar is normal.

Dr. McCullagh: You still think that, if these symptoms occur they are due to hypoglycemia?

Dr. Miller: Yes.

Dr. McCullagh: I agree.

Dr. Miller: What I am trying to say is that hypoglycemia in the older, mildly diabetic patient may not have the same obvious manifestations obtained with regular insulin. Therefore, the hypoglycemia should be watched for carefully.

Dr. McCullagh: It may produce only chronic fatigue.

Dr. Jordan: What is the pathologic-physiologic mechanism back of potassium depletion?

Dr. Browne: First of all, potassium tends to be lost from the intracellular water if cells break down. Therefore, under catabolic phenomena there will be a tendency for a loss of potassium from the body. After that has gone on for a certain period of time let us suppose that one is given glucose. This also happens, according to Dr. Thorn, in cases of Addison's disease treated with DCA. When one gives glucose, the potassium phosphorus for that matter tends to be deposited with the glycogen in the liver and elsewhere. An actual hypopotassemia may occur with a variety of signs and symptoms. At least part of the mechanism of potassium depletion is due first of all to its loss in the body associated with metabolism and secondly to the tendency to remove it by the use of glucose and insulin. There is a quite famous report on a diabetic child who, on recovering from coma, received 70 Gm. of sodium chloride per day. His blood pressure rose to about 170/110 and his diabetes disappeared. This happened spontaneously. When he ceased to eat, his blood pressure fell to normal and his diabetes reappeared. He then began to eat. He was taking in potassium. Subsequent raising of the sodium no longer led to this condition. It was only in the presence of a potassium poor or absent diet that this dramatic effect on carbohydrate tolerance occurred. I should like to know if anyone here has discovered what the mechanism of this is because it has always interested me. I feel that somewhere there is an explanation for a lot of things but I don't know what it is.

Dr. Jordan: We'll pass your question and any supplementary parts on to Dr. Lazarow.

Dr. Lazarow: I think I got into this because I want to amplify a little on what Dr. Browne said in relation to the glycogen story. It's been pretty fairly shown that for every gram of glycogen stored in the liver, it is stored with about 3 Gm. of water. Since water in the cell must be stored with electrolyte and since intracellular electrolytes are different from those which are present in the serum, namely high in potassium, when intercellular water is stored, intercellular potassium is stored as well.

Dr. Jordan: Do you have an explanation, Dr. Miller?

Dr. Miller: I was just as curious about that as Dr. Browne.

Dr. Jordan: Are there any acceptable books for the diabetic patient which may be used by him to supplement his medical supervision? Are there movie films available which may be instructive to groups of diabetics?

Dr. Schneider: One book which we have employed for a number of years is Joslin's "Manual for Diabetics." Dr. Henry John has a practical manual. There are other good ones.

Dr. McCullagh: Dr. Wilder has produced a good manual for diabetics; Dr. Bortz of Philadelphia produced one. There is a little book for patients called "The ABC's for Diabetics" with a great many pictures in it.

Dr. Miller: A book which we recommend is "Diabetic Care in Pictures" by Rosenthal. It has the advantages of having a profusion of pictures clearly done and also the text is not too complicated.

Dr. Jordan: Once three before meal blood sugars have been determined to be satisfactory on a given dose of insulin, will the relative blood levels remain the same on the same dose? How often should three a.c. blood sugars be done on an ambulatory patient to insure proper adequate control of the diabetes?

Dr. McCullagh: The answer to the first question is, "no," it will not necessarily stay put indefinitely. In fact, they don't stay put well at all. In some patients blood

sugars are always erratic and one of the policies perhaps in depending so much on blood sugars done before meals, or any other time for that matter, is that we know that they don't give us a picture which can be accepted as being constant.

The number of times, the frequency with which these tests should be redone is a matter of the judgment of the physician—it has to do with the severity of the diabetes. In general we like to have our patients come back to have the tests done a week or so after their first control and perhaps thereafter in three weeks or a month. The time they come back may vary between perhaps two and three months, as an average, and in less severe cases in four to six months.

Dr. Jordan: What is the relation of insulin to methionine metabolism?

Dr. Lazarow: In order to synthesize insulin it is necessary to have the constituents of amino acid which go into making the insulin molecule. The body is able to synthesize only about half the amino acids that are generally required and consequently an adequate supply of essential amino acids which the body cannot synthesize would be necessary. Since one of the constituents of insulin is cystine, which is a sulfur-containing compound and since probably the largest supply of sulfur-containing compounds enters the body as the amino acid, methionine, one would expect that at least requisite amounts of methionine or cystine would be necessary in order to insure insulin synthesis. The second aspect of the problem is the possible end relationship of methionine and glutathione. In the case of an alloxan diabetic animal, and it appears to be true following the injection of adrenocorticotropic hormone, there seems to be some relation between glutathione and diabetes. We have suggested that it may be an important prophylactic factor, but whether it is also true in human diabetes remains to be determined. However, if a glutathione factor should be important then methionine would also be involved since glutathione too contains cystine since it is probable that the major source of the sulfur of cystine comes from methionine.

Dr. Jordan: Can a patient get symptoms of hypoglycemia or resembling hypoglycemia with a relatively high blood sugar?

Dr. Miller: That is a difficult question. I think most of us have had the feeling that there are cases in which insulin reactions may occur at relatively high blood sugar levels. The converse is true also and we have much more evidence of that. The patients may be walking around with blood sugars as low as 30 and 40, particularly on protamine-zinc insulin without any obvious symptoms or signs of insulin reaction.

Dr. Jordan: Any other comment?

Dr. McCullagh: No, I agree with what Dr. Miller said.

Dr. Jordan: What are the EKG signs of hypopotassemia?

Dr. LeFevre: There are two major changes involving chiefly the S-T segment and the T wave. The usual changes are depression of the S-T segment and decrease in elevation of the T wave or flattening of the T wave.

Dr. McCullagh: Is there a prolongation of the Q-T segment?

Dr. LeFevre: It may or not be present. I don't think that it is as important as the depression of the S-T and T wave, although there may be some prolongation.

Dr. Jordan: How do you determine the initial dose of insulin?

Dr. Schneider: By trial and error. I think that the only point that is important is to emphasize again one thing about the administration of insulin. That is to remember always that insulin sensitivity may exist and it is always well to give the first dose perhaps a little smaller than you would be inclined to by the height of the blood sugar. The other factors that would determine the size of the dose of insulin, of course, would be the presence of complications, acidosis, infection, and so forth.

Dr. Jordan: Dr. McCullagh, how do you control insulin resistance?

Dr. McCullagh: You don't.

Dr. Jordan: What do you do when you have resistance? I think that is what the questioner means.

Dr. McCullagh: We just keep giving more and more insulin until we finally reach the point where the blood sugar is reasonably controlled. Sometimes that may take doses into the thousands of units per day. I have had one patient who required 1400 units per day. Such resistance may largely disappear which is a matter of mystery too.

Dr. Jordan: In other words, just keep going up until you get enough. That gets a little bit expensive sometimes.

Dr. McCullagh: It does, indeed.

Dr. Jordan: What is the proper procedure in mixing insulin for administration of insulin mixtures?

Dr. Miller: There are two methods—possibly three methods—which are being used. One is layering the insulin in a syringe, taking protamine zinc insulin first and adding the regular next. It is important, of course, to remember that you can't take insulin out of a sealed bottle without producing a vacuum. The air must be put in first. A good procedure is to put air in the regular insulin bottle and remove the needle. Then protamine zinc insulin may be obtained in the ordinary way, putting air in first and removing insulin. Then one can return to the regular insulin bottle and remove the insulin since the air has been previously introduced. This method sounds complicated but it is not nearly so complicated once it is tried. Another method which is unfortunately not available for most patients is that of having a premixed insulin. In this way you can get any insulin mixture desired: 2:1 mixture or 1:1 mixture and so forth. A few years ago Lilly Company supplied an oversized bottle which made it relatively easy to obtain any mixture required. At our hospitals—University Hospitals—we have a pharmacist prepare them. The average pharmacist often will not do it. There is no reason why the individual physicians could not mix insulin for their patients; a 2:1 mixture is the one most commonly employed at the present time.

Dr. Jordan: What are the indications and advantages of the 500 unit insulin?

Dr. Schneider: We still have too little experience in the use of 500 unit insulin, but the advantage would appear to be that those people with insulin resistance who require large doses of insulin can inject a smaller volume of solution.

Dr. McCullagh: It has a longer effect than if it were given in a weaker solution.

Dr. Jordan: Mason states, "In the case of the juvenile diabetic the blood cholesterol is a much better index of the completeness of the control than the blood sugar level." Is this the general belief today?

Dr. McCullagh: I think there is a great deal to be said on this point of view though I wouldn't go quite so far as to state it in those terms myself. I feel that the cholesterol is a valuable index of the control in the diabetic particularly when the blood sugars are erratic. We like to take blood cholesterols frequently in adults too, feeling that if the patient is out of control most of the time and just follows his diet two days before he is coming to see us, we may find that out from a high blood cholesterol when the blood sugar is normal.

Dr. Schneider: I agree with Dr. McCullagh. I think that perhaps a better criterion for determining satisfactory control of diabetes in children is their rate of growth, their weight, and their general sense of well being—their total nutrition in other words, regardless of what the cholesterol is.

Dr. Jordan: You think that is better than either laboratory test?

Dr. Schneider: I do.