DIABETES

On March 17, 1949, the Frank E. Bunts Educational Institute presented a continuation course on Diabetes. There follow abstracts of the proceedings of this course.

THE PHYSIOLOGY OF INSULIN

E. Perry McCullagh, M.D.

Insulin comes from the islets of Langerhans, which are groups of about 30 cells weighing 1/120 of the weight of the pancreas. These cells are of several types; the alpha and beta cells are granulated, suggesting secreting power. The fact that insulin arises in the islet cells is supported by the fact that it is present when enzyme tissue is degenerated; moreover, it is present in adenomata or carcinomata of islet tissue. Its production is influenced either by pituitary extracts or alloxan, the effects of which are shown in microscopic changes of the islet cells, especially the beta cells.

Insulin, first produced in extracts by Banting and his co-workers in 1922, was crystallized by Abel in 1926. It is an interesting fact that it contains zinc. The hormone is a polypeptide of approximately the molecular weight of egg albumen. One of the most potent factors regulating insulin production is the amount of glucose reaching the pancreas in arterial blood.

Some of the important functions of insulin may be listed as follows:

1. It regulates blood glucose levels.
2. It effects the storage of glycogen in liver and muscles.
3. It influences utilization of sugar by the tissues.
4. It increases fixation of amino acids in tissues for production of protein.
5. It has indirect action on hepatic ketogenesis and consequently on blood ketones and fats.

Of physiologic importance is the fact that insulin normally flows directly to the liver.

The chief effect of blood glucose is by virtue of affecting glucose deposited. There is also good evidence that insulin prevents protein breakdown (productive of more sugar) within the liver. In this and in similar ways insulin effects nitrogen excretion.

In the absence of insulin there is a rise in the level of blood glucose, amino acids, urea, creatine and creatinine; also great shifts in blood electrolytes including sodium and potassium. Phosphorus is intimately affected since phosphorus is closely connected with the transfer of glucose from blood to tissues and in the preparation of glucose for immediate oxidation. When a fall of blood potassium occurs as a result of insulin withdrawal, myocardial changes occur which are shown in the electrocardiogram as a long Q-T interval with broad T waves, and in some cases prominent U waves.

It will become increasingly important to learn ways of measuring the amount of insulin in the blood. Current methods under examination include the measurement of transfer of radioactive phosphorus in an exchange between free phosphorus and that found in phospho-creatin in a muscle mixture treated with insulin. Another method is based on the hypersensitivity to insulin found in an hypophysectomized, adrenalectomized animal, or a method in which insulin is tested in an animal which is hypophysectomized, adrenal-medullectomized and made alloxan diabetic.

The recent work of the Coris may point to the mode of action of insulin. According to this theory, the enzyme hexokinase (with which adenosine triphosphate converts glucose into glucose 6 phosphate which can be metabolized) is inhibited by anterior pituitary or by adrenal extract. This inhibition is antagonized by insulin. Unfortunately as yet this reaction cannot be translated freely into clinical medicine.

THE DIAGNOSIS OF DIABETES

R. W. Schneider, M.D.

In severe cases the diagnosis of diabetes is simple, being recognized by polydipsia, polyuria, and weight loss and confirmed by finding glycosuria and hyperglycemia. In early or mild cases, symptoms are always absent. Glycosuria is often the only early sign and may appear so intermittently that diabetes may be too quickly eliminated when the urinalysis is negative. A specimen should be obtained one to two hours after a heavy meal since the fasting specimen in mild cases is apt to be negative. It has been estimated that about 5 per cent of cases have no glycosuria. Recognition of these cases depends entirely upon the presence of an elevated blood sugar. This includes individuals with "high renal thresholds" as well as those with early impaired carbohydrate tolerance.

In a few borderline cases blood sugar levels taken two or two and one half hours after a hearty meal may be abnormal, when fasting or four hour tests are normal. Duncan mentions a patient with a normal fasting blood sugar who was seen a few months later in coma with a blood sugar of 1260 mg. per cent.

Glucose tolerance tests may need to be employed in borderline cases and extreme care exercised in their proper interpretation. Occasionally, the diagnosis will best be deferred until more complete evidence can be obtained. The glucose tolerance test should be reserved for the mild cases which cannot be properly recognized without it, and to exclude the suspicion that diabetes is present when it does not exist. All too frequently, glucose tolerance tests are obtained on patients already known to have glycosuria and hyperglycemia. In such instances, the patient has been subjected to additional expense and inconvenience not to mention the possibility of some harm, and the physician emerges with no more precise information than he already possessed.

Sugar in the urine is presumptive evidence of diabetes. Approximately 90 per cent of cases are recognized in this way. The separation of diabetes from renal glycosuria must depend upon random blood sugar determination and, if necessary, a glucose tolerance test. Separation from other causes of glycosuria must also be considered. Temporary glycosurias may appear during the course of infection or secondary to thyroid, adrenal, liver and pancreatic disorders. Others follow brain injury,encephalography, emotional crises, or after the administration of drugs. False positive results occur in other melliturias such as from levulose, pentose or fructose as well as in alkaptonuria. The confirmation of the diagnosis of diabetes by the determination of an elevated blood sugar accompanying glycosuria will avoid such serious errors as inducing insulin shock in individuals with renal glycosuria or in depriving patients from securing life insurance at normal premiums when diabetes does not exist.

When glycosuria has been observed, the urine must also be examined promptly for acetone since its presence is a matter of great and immediate therapeutic significance.

The interpretation of borderline blood sugar levels is difficult due to lack of agreement about normal and abnormal values. Interpretation is further confused because of technical difficulties in methods.

We regard blood sugar levels of 120 mg. per cent or above when fasting or two and a half hours after food as being abnormal, but permit levels of 200 mg. per cent one-half to one hour after eating. Most insurance companies have regarded levels over 120 fasting as being abnormal, but vary in accepting levels between 160 and 225 as the upper limit one hour after food. When more widespread acceptance of one method of blood sugar determination has been obtained there will undoubtedly be uniformity of opinion regarding the normal limits of blood sugar levels.

In the use of the glucose tolerance test for the diagnosis of diabetes, there is no uniformity of opinion as to the method to be employed or its proper interpretation. We

have used the 100 Gm. single dose, oral glucose tolerance test routinely except in children in whom the amount has been reduced. Blood and urine samples are collected fasting and at one-half, one, two, three, and four hour periods following administration of glucose. We regard the test as being normal when the blood sugar has returned to 120 or less by the end of two and one-half hours. We regard the peak of the curve as the least single important diagnostic feature and place greater emphasis upon the speed of its return, viewing a lag up to three or four hours as important.

In the interpretation of abnormal glucose tolerance tests the effects of obesity, age, exercise, gastrointestinal absorption, disturbances within the pituitary, thyroid and adrenal as well as the liver, are the more important factors. In addition, the diet preceding the performance of the glucose tolerance test has a bearing upon its results. It is the effect of the previous diet upon the result of the test which is most likely to be overlooked. Normal persons who are starved or fed diets low in carbohydrates will display diabetic types of glucose tolerance curves. This factor can be eliminated by the administration of 250 to 300 Gm. of carbohydrate for three or four days before performing the test.

RECENT DEVELOPMENTS IN EXPERIMENTAL DIABETES

*Arnold Lazarow, M.D.**

Diabetes, a disease which is characterized by hyperglycemia and impaired glucose metabolism, has been produced in experimental animals by a wide variety of procedures. These include total or subtotal surgical removal of the pancreas, the injection of massive amounts of anterior pituitary or adrenal cortical hormones, and the administration of alloxan. In the intact animal there is an antagonism between the pancreas on the one hand and the pituitary and adrenal cortex on the other. Although metabolism is normal when all of these glands are present and functioning, an imbalance between the pancreas on one hand and either the pituitary or adrenal cortex on the other produces diabetes. Such an endocrine imbalance is produced by the removal of the pancreas or by the injection of excessive amounts of the anterior pituitary hormone. Although the injection of A.P.E. produces its initial effect by action on the liver, the long continued administration of anterior pituitary hormone produces a secondary degeneration in the beta cells of the pancreas and thereby produces a permanent or secondary pancreatic diabetes.

The discovery that alloxan produces diabetes in experimental animals (Dunn, Sheehan and McLetchie, Lancet 1:484, 1943) has stimulated a great deal of work on the etiology of diabetes. It has been shown that glutathione (Lazarow, Proc. Soc. Exper. Biol. and Med. 61:441, 1946) plays an important role in determining the susceptibility of rats to alloxan diabetes. When the glutathione content of the body is increased, by the prior injection of this sulfhydryl compound, rats are completely protected against a diabetogenic dose of alloxan; by contrast when the glutathione stores in the body are depleted by the injection of ascorbic acid, rats become more susceptible to alloxan.

Alloxan reacts with the sulfhydryl group of glutathione and with sulfhydryl groups of essential enzymes. It is suggested that the diabetogenic action of alloxan may be due to enzyme inactivation occurring as a consequence of sulfhydryl enzyme inactivation. Although alloxan selectively destroys the beta cells in the pancreas, it is also capable of destroying many other cells. Perhaps the specialization of the beta cells for the synthesis of insulin may predispose these cells to alloxan by lowering the beta cell gluta-

thione content. Cysteine, a sulfhydryl amino acid, is a precursor of both insulin and glutathione. (Twelve per cent of the amino acids of insulin are cysteine.) It has been calculated that if all of the cysteine contained in the glutathione of the beta cells of man were available for insulin synthesis, less than 20 units of insulin would be formed. This is but a fraction of the daily insulin requirement of man. Since the glutathione in the various cells of the body is not in rapid equilibrium the specialization of the beta cells for the production of insulin may result in a localized depletion of cysteine and glutathione and thereby may render these cells more susceptible to alloxan.

It is further suggested that the degenerative changes observed in the beta cells of the pancreas following subtotal pancreatectomy or following anterior pituitary hormone or massive glucose injection may in part be due to a localized depletion of the beta cell glutathione occurring as a consequence of an increased rate of insulin synthesis. Thus any factor which increases the rate at which insulin is synthesized by the beta cells would thereby tend to deplete beta cells cysteine and glutathione and thereby make these cells more susceptible to the action of toxic or metabolic factors which may normally appear within the human body.

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SELECTION OF DIET

R. W. Schneider, M.D.

The optimum diet for the diabetic is that which will keep him well and strong, at the same time not permitting his weight to rise or fall far from ideal. It should be palatable and satisfying. Diets high in carbohydrate and low in fat or the reverse are not generally palatable. Men generally like diets higher in meat and are often not satisfied until 90 Gm. of protein per day is permitted.

The diet must also supply correct caloric requirements of the individual. It must be properly balanced with carbohydrate, protein, fat and total calories and should also meet the long-time requirements in vitamins and minerals. A gain or loss in weight will determine how correctly such requirements are being satisfied.

The selection of the diet best suited for the individual patient is the first problem which must be settled by the physician. One fundamental principal has been well established, namely, the avoidance of over-feeding. Prolonged over-nutrition often leads to fatty liver and this may increase the susceptibility to infection and coma. Certainly, diabetes is one penalty of obesity and the mortality rate in diabetes beyond 45 increases with the degree of excessive weight. Furthermore, Newburgh has shown that glucose tolerance tests may be returned to normal in more than three-fourths of those adult obese hyperglycemic patients who undergo adequate weight reduction.

It matters little what means of measurement of food is adopted: scales are best in the end but household measures in cups and spoons will serve when scales are not available. Accurate weighing of the food will repay the patient, however, by enabling him to estimate more accurately food quantities when he is without means of more accurate measurement.

In selecting the diet for the obese patient, the principle consideration is the total caloric intake. We commonly employ a diet supplying 100 Gm. carbohydrate, 62 Gm. protein and 50 Gm. fat, allowing a total intake of 1098 calories per day. We have employed this diet simply because it can be applied in the majority of obese subjects. The caloric intake may be increased or decreased in these obese individuals depending upon their customary activity.

Larger caloric prescription must be arranged for those with normal or subnormal

weights. The variations introduced by age, sex, height, basal metabolic rate and level of daily activity must be considered. The best ultimate guides are the general health in terms of weight and strength, and in children, growth. Periodic adjustment to higher or lower diets will frequently depend upon progress. Larger diets of necessity must be employed in children, manual laborers, and malnourished subjects.

General bodily structure may modify the prescribed caloric intake at times. A helpful rule is to allow 10 per cent additional weight for large-framed individuals and to substract 10 per cent for those of light frame.

Additional increments of food to allow for occupation may be permitted as follows: 10 per cent additional for people at room rest, 15 per cent for light work, 20 per cent for average work, 30 per cent for heavy work, and for growing children and manual laborers 40 to 50 per cent.

In general, we tend to maintain carbohydrate intake between 100 to 250 Gm. per day. We allow sufficient fat to keep the diet palatable and yet not overloaded. In our basic diet, the daily intake permits three servings of fruit, one egg, 500 Gm. milk, 15 Gm. butter, 100 Gm. of cereal or one slice of bread (15 Gm. carbohydrate and 3 Gm. protein).

As the diet is raised in bread or its equivalent, butter is also increased in increments of 10 Gm. Fat intake generally ranges from 50 to 150 Gm. per day, seldom higher. Protein is raised from 90 to 120 Gm. in manual laborers and in patients with liver disease or hyperthyroidism. In the past few years, we have also advocated 120 to 140 Gm. of protein per day in patients with diabetic retinopathy in an attempt to combat the hypoalbuminemia common to the majority of them. Occasionally advanced renal insufficiency seems to contraindicate its use, but seldom have we seen increasing azotemia following the addition of high protein feedings in such cases.

Our usual practice has been to divide the total quantity of food for the day into three equal parts, but many clinicians advocate supplementary feedings between meals and at bedtime in order to distribute the metabolic load more evenly over a greater number of hours. When protamine-zinc insulin is used, bedtime feedings are especially valuable. For individuals who do not require insulin, we distribute the available glucose into three meals permitting 25 per cent of the total for breakfast, 35 per cent for lunch and 40 per cent for the evening meal. When protamine-zinc insulin is used, the available glucose is distributed into four feedings, 20 per cent being given for breakfast, 30 per cent for lunch, 40 per cent for dinner, and 10 per cent at bedtime. We employ globin insulin infrequently, but when it is used the distribution is changed to 20 per cent for breakfast, 40 per cent for lunch, 10 per cent at the three o'clock feeding in the afternoon, and 30 per cent with the evening meal.

CALCULATING AND PLANNING DIABETIC DIETS

Marjorie R. Curry, B.S.

Good sources of food analyses are:

1. Food and Beverage Analyses by Milton Bridges.
2. Food Values of Portions Most Commonly Used by Bowes and Church.
3. Fundamentals of Nutrition by Mary Schwartz Rose.
4. Various Gov't. Bulletins from the Dept. of Agriculture for example: Miscellaneous Publication No. 572.

We build all diabetic diets on a basic meal plan. The total basic diet contains carbo-

hydrate—100 Gm., protein—64 Gm. and fat—50 Gm. to a total of 1106 calories. The diet contains for breakfast:

	carb.	*prot.*	*fat*
1 serving of fruit	10		
1 egg (soft-cooked or poached)		6	6
1 slice of bread (Preferably whole wheat)	15	3	
½ square of butter			4.2
½ glassful whole milk	5	3	4
for luncheon:			
3 ounces of cooked lean meat or an equal substitute		18	7.5
1 cupful cooked 5% vegetable	10	2	
1 cupful raw 5% vegetable	5	1	
½ square of butter			4.2
1 glassful of milk	10	7	8
for dinner:			
3 ounces of cooked lean meat		18	7.5
1 cupful cooked 5% vegetable	10	2	
½ cupful 10% vegetable	10	1	
½ square of butter			4.2
½ glassful milk	5	3	4

This diet provides the essential foodstuffs for protective nourishment, that is enough calories for maintenance, adequate protein containing essential amino acids, carbohydrate and fat to make up the caloric requirements, adequate bulk, vitamins, minerals, and certain fatty acids.

As the diet prescription is increased, additions of bread, cereals, cream, and other foodstuffs are made. For example the addition of one slice or 30 Gm. of bread adds 15 Gm. of carbohydrate (50 per cent of bread is carbohydrate) and 3 Gm. of protein bringing the total carbohydrate to 115, protein to 65, leaving the fat at 50, and yielding 1170 calories.

If the prescription of C 130, P 68 to 1800 calories is given, we calculate the fat content to 112 Gm. Our calculation then would add two slices of bread to the basic diet and for 62 added Gm. of fat, we might change the milk allowed at breakfast and dinner to 20 per cent cream adding 32 Gm. of the fat. The remainder might be added as butter (an additional 35 Gm. or 3½ squares) yielding 29.6 Gm. of fat.

This diet is given in just three meals daily. The type of insulin and its action also affects our meal planning scheme.

After the diet is arranged to fit the medical prescription, the personal equation enters the picture. The patient's food likes and dislikes must be accounted for as well as his ability to comprehend a diet instruction and his ability to purchase and prepare these foods. All diet instructions are given individually. When a language problem exists, we usually request the aid of one of the family as interpreter. For husbands, we frequently ask the wife to sit in on the instruction as she does the actual meal preparation.

Our first instruction to the patient is usually given in household measures unless specifically ordered as a weighed instruction. The average patient is familiar with cupfuls and glassfuls while gram weights are altogether foreign. As the patient learns the diet and becomes adjusted to a diabetic routine, we encourage him to buy gram scales and weigh his food.

For measuring, the term cupful always means an eight ounce measuring cup. A

glassful is six and one-half ounces. These measures work well with two exceptions, bread and meat. For these we use ruler measurements suggesting that they cut models for their use at home or as in many cases, where household scales are available, the patient weighs his bread and meat while measuring other foods. In all instructions, however, are discouraged because they are difficult to prepare accurately.

Each patient has definite food preferences so lists of fruits, vegetables, and meats permit him to select those which he prefers. The substitution list may be used to convert bread to potato or milk to meat and fruit or to alter the general outline so that he will not become tired of certain foods. In the case of foreign patients, we attempt to teach them how to fit their native dishes to their prescription. Complicated mixtures, however, are discouraged because they are difficult to prepare accurately.

During the actual instruction, major points of food preparation are emphasized. Fruits should be canned without sugar or fresh fruit in season. Meats should be either broiled, roasted, or stewed. Fat and bone should be trimmed from the meat before measuring because our calculations are on cooked lean meat (edible portion). Fat is one of the important factors of a low caloric diet. All fats (margarine, food oils, cooking fats, and bacon drippings) are permitted on our diets, but they must be used as direct substitutes for butter, and measured just as accurately. In vegetable preparation, baking, boiling, or steam pressure cooking may be used. Any fat used for seasoning these vegetables must be taken from the butter allowance.

In all cookery, salt, pepper, vinegar, saccharin, and spices may be used as desired unless there are other therapeutic restrictions on the diet. Water, black coffee, clear tea, and clear fat-free broth may be used in unlimited quantities.

Two supplements which we use for desserts are the diabetic gelatin called D-Zerta which has so little food value that it is negligible, and Junket tablets containing no food value, but which will congeal milk to a soft custard consistency. The use of all other special foods, such as diabetic puddings (so-called), diabetic cookies, and candies, is discouraged. If a patient insists upon using them, we ask them either to check the product or the label so that the food values can be computed.

Menus are not written for our patients. We urge them to write their own, and then to let us go over the menus with them. The primary reason for this is that it helps make the diet as flexible as possible. A general outline will permit each patient to fit his food prescription to his individual budget, to make the most of his marketing facilities, and to appease his own appetite within reason.

The most important objective is to teach each diabetic patient the importance of his diet, and then to make him want to learn and understand it.

SOME PATHOLOGIC ASPECTS OF DIABETES

John B. Hazard, M.D.

Though diabetes may produce very striking changes in many tissues of the body, the organ responsible for the production of insulin may show relatively little or no change. This was even a more common finding before methods were developed for separation of the alpha and beta cells of the islets.

Though there may be no demonstrable pathologic change in the pancreas, in a large percentage of cases abnormalities may be found if special technics are used in addition to routine procedures. The beta cells of the islets can be estimated only after special fixation and a staining procedure such as that of Gomori. Since the satisfactory fixatives for this are not in common use in most pathologic departments review of much of the material collected in the past cannot be evaluated in this respect. However, when such studies have been made, beta cells have been found to be absent, greatly reduced, moderately reduced or normal. In a recent series reported by Bell (Proc. Am. J. Path 22:

631, 1946), the beta cells were absent or greatly reduced in 21 of 30 cases of diabetes. Gomori (Am. J. Path. 17:395, 1941) reports a marked reduction in the beta:alpha ratio. A second more common finding in the pancreas is hyalinization of the islets which may occur in 30 to 50 per cent of the cases, depending somewhat upon the patient's age. In older patients, of course, it may occur without the presence of diabetes. A third and much less common histologic lesion is nuclear pyknosis in the islet cells. Uncommon diseases which may be associated with diabetes are hemachromatosis, extensive carcinoma of the pancreas or even, more rare, large cyst adenoma of the pancreas.

The increase in the incidence of arteriosclerosis in diabetics is well known. Involvement of the coronary arteries results in four times as many deaths due to arteriosclerotic lesions of these vessels as are found in non-diabetics in corresponding age groups. The increased arteriosclerotic involvement of coronary arteries also reverses the sex ratio in regard to myocardial infarction.

In the peripheral arteries, reduced blood supply leads to gangrene, intermittent claudication, and probably contributes to an increased susceptibility to infection so that minor injuries to the skin may lead to serious suppurative disease. The occurence of suppurative tenosynovitis with extension of exudate along the tendons of the foot and into contiguous soft tissues is one of the serious results of the reduced ability to combat bacterial intrusion.

In the original series of 8 cases of intercapillary glomerulosclerosis reported by Kimmelstiel and Wilson (Am. J. Path. 12:83, 1936), all patients were middle aged, diabetics with hypertension, albuminuria and edema. There have been many others recorded since and the facts may be summarized: approximately 40 per cent of diabetics exhibit the lesion in some degree; in a severe degree it occurs only in diabetics. The incidence appears to increase with the duration of diabetes. Though hypertension was reported originally in all cases, subsequent reports indicate only 50 per cent with hypertensive disease. Grossly, the renal lesion much resembles that found in arteriolar nephrosclerosis, with pallor of varying degree and with a coarsely pitted surface and thin cortex. Histologically, it is characterized by small hyaline foci between the capillaries of the tuft, of varying size and number. Since amyloid is deposited in a similar location, it must be differentiated by a special staining technic to avoid possible misinterpretation of the nature of the intercapillary substance.

Acute renal infection is the cause of death in diabetics about four times as frequently as it is in a corresponding nondiabetic group. In a small portion of patients with diabetes, approximately 3 per cent as judged by past reports, a diffuse necrotizing lesion involves the renal papillae. It is of serious import as most all the patients have died, though this may be altered by modern chemotherapy. In its gross aspects, the lesion is manifest by dull, grayish to yellowish, necrotic renal papillae with sloughing tissue masses that are shed into the renal pelvis and thus produce a defect which may be evident on pyelographic examination. Histologically, there is diffuse necrosis of the tissue of the papillae, without cellular reaction or with a reaction almost limited to plasma cells. The agent is most often Staphylococcus aureus. Women develop the lesion more commonly than men.

The peripheral nerves in a small percentage of diabetics show diffuse or patchy degenerative changes associated with sclerosis of the intraneural vessels. There may be a neurolemmal proliferation. The symptoms are generally sensory, and are usually referable to the lower extremity. Trophic lesions are, of course, common in those who develop this neural lesion.

Changes in the bones and joints of the feet consist of periarticular thickening, and destruction of bones and joints so that metatarsal or phalangeal bones may be represented merely by small bone spicules lying in a fibrous matrix.

Diabetic retinopathy is among the more serious lesions occurring in diabetes. It involves the veins and capillaries of the retina as distinguished from the arterial lesions evident in hypertensive disease. The changes consist variously of venous congestion, hemorrhages, phlebosclerosis, over-growth of new veins (retinal pannus), deposition of lipoid in the nerve fiber layer and exudates of varying type and severity in the deep retinal tissues. Later in the disease there is detachment of the retina, degenerative changes in the retina and a thick vascular network. Cholesterol may be deposited in the vitreous and in the fluid beneath the retina. There is irreversibility of the more severe changes.

In typical form cataracts occur bilaterally and in severe diabetes; early it may be a reversible disease. There is opacity of the lens due to subcapsular degeneration, "water fissures" and repair proliferation.

CHOICE OF INSULIN PREPARATION

E. Perry McCullagh, M.D.

From a practical standpoint, there are four types of insulin from which to choose. They are:

1. Protamine-zinc insulin.
2. Regular and crystalline insulin.
3. Insulin mixtures.
4. Globin insulin.

Protamine-zinc insulin, first introduced in 1936 by Hagedorn, is the most popular insulin. Zinc originally added to increase the stability of the mixture has been found to prolong its effect. A single injection of this insulin is active in three or four hours and acts for more than twenty-four hours.

Regular (amorphous) and crystalline insulin have similar effects. They represent the true hormone, active within a few minutes, with a peak effect in four hours and action from a single dose which is over in about eight hours. Larger doses have relatively longer effects and concentrations as high as 500 units have prolonged activity approximating that of protamine-zinc insulin. Regular or crystalline insulin is the insulin of choice in emergencies such as acidosis, infection, trauma, surgery, and other complications.

Mixtures of protamine-zinc insulin and regular insulin have been used because it is found frequently that protamine-zinc insulin alone may fail to control blood sugar levels within the first few hours after administration. All mixtures produce modified effects of both. A new insulin mixture, designated N.P.H. 50, is being examined with the thought of having a ready-made preparation generally available.

Globin insulin is of less practical value than the others, failing often to control blood sugar levels in the first few hours after it is prescribed. If given in the morning, it tends to cause hypoglycemia in the midafternoon and may still fail to maintain normal fasting blood sugar levels.

The available glucose of the diet may be distributed by meals to meet the timing of the maximum insulin effect. We use the following distribution:

Regular or crystalline insulin	30	35	35	
Protamine-zinc insulin	20	30	40	10 H.S.
Mixtures	Any distribution suited to the individual			
Globin insulin	20	40	10 (p.m.)	30

Who Needs Insulin?

Among those who usually need it are the following:

1. Patients in acidosis.
2. Those with acute infections.
3. Patients with chronic infections.
4. Most diabetic children.
5. Patients requiring a high caloric diet.
6. Those with initial blood sugar levels over 300 mg. per cent.

Some may do as well without insulin as with it, although the number is relatively few. They include:

1. The very old patient.
2. The extremely mild diabetic.
3. The obese patient willing to follow a reducing diet who has a blood sugar level of 200 or less fasting.

Some Principles in the Use of Insulin

If the fasting blood sugar level remains high on the prescribed diet protamine-zinc insulin may be given and increased to produce a normal fasting level. Relatively smaller doses must be given to the very young, the very old, and the emaciated patient. If the fasting sugar is normal and the blood sugar level rises above normal at noon or later, regular insulin may be added as a separate dose or in a suitable mixture adjusted to individual needs.

Globin insulin is most useful in those patients with normal fasting sugar levels and high levels later in the day. In erratic diabetes in which control is unpredictable extra insulin may be added according to urine sugar if it is judged on specimens obtained within a half hour after having emptied the bladder. Formulas for patient use refer to the yellow, orange or red Benedict's tests, and may be written $\frac{\text{Y O R}}{3\ 4\ 6}$ or increased to any necessary amount such as $\frac{\text{Y O R.}}{5\ 10\ 15}$ No extra insulin is given at bed time if protamine-zinc is used.

INSULIN MIXTURES

*M. Irving Sparks, M.D.**

The purpose of insulin mixtures is to provide an "intermediate" insulin so that patients may be controlled by one daily injection. By mixing varying proportions of regular and protamine zinc insulins a graduated series of "intermediacy" can be obtained— extending from almost pure regular insulin effect on the one extreme to pure protamine zinc insulin effect on the other. The action of mixtures is that of an "intermediate" insulin, not merely a summation of the actions of its component parts.

There are four preliminary explanatory points. A. Protamine Zinc Insulin—protamine and insulin combine chemically, therefore in definite proportions (0.67 mg. of protamine per 100 units of insulin). But in the commercial preparation of P.Z.I., the manufacturers add almost twice as much protamine as is necessary (1.25 mg. protamine per 100 units). It therefore follows that commercial P.Z.I. can take up and convert to P.Z.I. almost its equivalent in unitage of regular insulin. In other words, 10 units P.Z.I. + 10 units regular = 20 units P.Z.I. This is not strictly accurate, but it is close enough to allow of the general rule—that to obtain any intermediate effect, there must be at least as much regular as protamine zinc insulin (by units) in the mixture.

B. Mixtures of two types have been recommended, and either one is indicated only when protamine zinc insulin by itself is not adequate.

1. Fixed Mixtures—when mixtures are indicated some workers have advocated using only one of the possible variations. Mixtures of 3:2 or 2:1 (regular: P.Z.I.) are the ones most recommended.

2. Variable Mixtures—here the proportions used are varied according to the needs of the individual patient. And the needed proportions vary widely not only from patient to patient, but in the same patient from time to time.

Each diabetic patient presents an individual problem which can be met better with a flexible than with a fixed method. Variable mixtures are therefore preferred.

One further point in favor of "variable" as opposed to "fixed" mixtures is mentioned under diet.

C. Diet—the diet used for "mixtures" is the same as for protamine zinc insulin alone, namely three approximately equal meals and a bed-time feeding. Breakfast may be made smaller if desired. With "fixed mixtures" it is more often necessary to use a mid-afternoon feeding than with "variable mixtures." Indeed with the latter it is only rarely required.

D. Method of checking—the one found to be the best is the one advocated by Dr. H. John, for it gives the picture throughout the day. It consists of taking sugar before each of the main meals (three a. c. blood sugars) on the day of check. The patient should be on any one given dose of insulin for at least two days before the check is made.

The procedure of regulating diabetes is as follows:

1. Put on adequate diet.
2. Then three a. c. blood sugars.
   a. if these adequate—no further treatment.
   b. if these high—put on 20 or 30 units P.Z.I.
3. Then three a. c. blood sugars
   a. if all about same level continue P.Z.I. increasing by 10 to 20 units at time until desired level of blood sugars is obtained.
   b. if spread of more than 100 mg.—change to mixtures. This applies regardless of the actual height of the blood sugars.

Graphs were shown illustrating the use of mixtures from which the following rules were deduced.

1. Use more regular than protamine zinc insulin.
2. The fasting blood sugar is the indicator as to whether the P.Z.I. should be increased or decreased.
3. The noon and afternoon blood sugars are the indicator for increasing or decreasing the regular insulin.

The first rule is not an invariable one, for occasionally patients are seen who obtain an intermediate effect from mixtures containing less regular insulin than P.Z.I.

Variable mixtures may be made up in either of two ways.

1. In the syringe each morning.
2. The proper amounts of each sufficient for 10 to 20 doses put into a bottle; the daily total dose being withdrawn each morning.

Most patients seem to prefer the former method, nor have any of them had any technical difficulty in using the mixtures.

Mixtures are needed more frequently when the total dose is over 30 units per day. But they have been used to advantage in total doses of from 15 to 90 units.

Almost 90 per cent of diabetic patients needing insulin can be adequately controlled by one injection a day. Fifty per cent by P.Z.I. alone, the remainder by mixtures.

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COMPLICATIONS RESULTING FROM INSULIN ADMINISTRATION

A. Gold, M.D.

Complications resulting from insulin administration are:

I. Physiological
   - A. Hypoglycemia
   - B. Insulin edema
   - C. Insulin presbyopia

II. Abnormal
   - A. Allergic
     1. Local
     2. General
   - B. Infection
   - C. Etiology unknown
     1. Insulin hypertrophy
     2. Insulin atrophy
   - D. Insulin resistance

The education of the diabetic patient in the recognition of and preparedness for hypoglycemia is important. Danger of permanent brain damage from prolonged insulin coma must be kept in mind.

Obese patients not infrequently complain of symptoms resembling those of hypoglycemia when, in fact, the blood sugar is normal or elevated. This should be demonstrated to the satisfaction of patient and doctor by doing blood sugar estimations during any suspected reactions.

In the absence of glucose for intravenous use, the patient in insulin coma may be given epinephrine in 1 c.c. dosage.

General or local edema of the face may occur shortly after beginning insulin treatment, especially in severe diabetics. This is due to rapid changes in water and mineral metabolism associated with the improved carbohydrate metabolism and subsides spontaneously. Changes in refraction are due to the same cause.

Localized swelling, pain, and tenderness at the site of insulin injection occurs frequently during the first few weeks of insulin treatment. The technic of injection should be gone over with the patient to establish whether he has been giving himself injections partially intradermally rather than subcutaneously. If such reactions persist after several weeks, crystalline insulin alone should be tried and in the strongest concentration available.

Anaphylactic reactions to insulin are fortunately extremely rare. The acute attack should be treated with intramuscular epinephrine, ½ c.c. repeated in twenty minutes if necessary. This should be followed by the use of an antihistamic such as pyribenzamine. Desensitization should be started as soon as possible. The rapid technic consisting of intradermal injections every fifteen minutes beginning with 1/1000 unit and doubling the dose each time unless a wheal appears when the last dose is repeated. When 1 unit can be given intradermally without wheal formation, subcutaneous injections should be started.

Insulin hypertrophy and atrophy are local reactions occurring in the subcutaneous tissues in areas in which insulin has been injected repeatedly. They may be avoided by teaching the patient to vary the site of injection according to a definite routine.

Insulin resistance may be associated with infection, acidosis, hormonal antagonists, allergy, or diffuse hepatic disease. Signs of hyperthyroidism, acromegaly, Cushing's syndrome and pheochromocytoma should be looked for. In spite of all investigations possible, in a majority of cases the cause remains undetermined. It is important to give

as much insulin as needed—which has been known to go as high as 2000 units daily—to prevent ketosis. *U500* insulin is helpful when dosage is high. Not infrequently resistance subsides spontaneously over a period of months.

PANCREATIC DISEASE AND DIABETES

Charles H. Brown, M.D.

The pancreas is intimately related anatomically and physiologically to the liver and may be said to be its guardian. Depancreatized dogs, patients with pancreatic steatorrhea, diabetic patients, particularly the juvenile type, frequently have fatty infiltration of the liver. Adequate doses of lipotropic substances such as lecithin, choline, and methionine, and the pancreatic hormone lipocaic decrease this fatty infiltration.

The relationship of disease of the pancreas to diabetes has long been and still is a major problem. The discovery of insulin was believed by many to have solved this problem. This is not the case as is shown by the fact that a considerable number of diabetics require more insulin than the 30 to 50 units required by patients who have had complete pancreatectomies.

The relationship of carcinoma of the pancreas to diabetes presents two problems. First, it is unlikely and rare that carcinoma of the pancreas causes true diabetes, although there may be changes in the glucose tolerance curves due to malnutrition, impaired liver function or other factors. Second, carcinoma of the pancreas does occur more frequently (4 to 6 times) in diabetics than in non-diabetic patients. The relationship of carcinoma of the pancreas to diabetes is similar to the relationship of carcinoma of the liver to cirrhosis.

Pain is present in about 80 per cent of the patients with carcinoma of the pancreas. Jaundice is present in about two-thirds of the patients; loss of weight is rapid and pronounced. Fatigue, weakness, nausea or vomiting, anorexia and constipation are other symptoms that are present in about one-half the cases. Diarrhea and psychoneurotic symptoms are present in about 10 per cent of the patients. Thrombophlebitis is common in this disease. On physical examination, a gallbladder is palpable in about one-third of the cases, a mass in about 15 per cent and ascites in about 15 per cent. Roentgen-ray examination may show: 1. widening of the duodenal loop. 2. inverted figure 3 sign and deformities of the second part of the duodenum, and 3. displacement of the stomach and other organs.

Calculus formation in the pancreas as a cause of diabetes is uncommon. However, diabetes is present in one-third to one-half of the patients with pancreatic lithiasis. Pain is usually present and is apt to be severe. Steatorrhea exists in about one-half of these patients. The clinical diagnosis is entirely dependent on the demonstration of opacities in the region of the pancreas on the x-ray film.

Acute pancreatitis is frequently accompanied by transient changes in the glucose metabolism and in transient glycosuria. Approximately 2 per cent of patients with acute pancreatitis will develop permanent diabetes. There are many milder cases of acute pancreatitis that may be confused with other abdominal catastrophes that require surgery. Surgery is contraindicated in acute pancreatitis, since 50 per cent of those subjected to surgery during the acute stage die. Consequently, it is advisable to obtain routinely serum amylase or diastase determination on every patient who has an abrupt onset of upper abdominal pain.

Chronic pancreatitis is an ill-defined clinical entity in which there is chronic fibrosis of the pancreas due to a diverse variety of conditions. Biliary tract infection, duodenal ulcer, obstruction of the pancreatic ducts by calculi or neoplasm, chronic alcoholism, hepatic cirrhosis, acute infection, and acute pancreatitis may all cause chronic pan-

creatitis. One might suspect this condition in any patient who has three of the following: 1. diabetes, 2. large voluminous stools, 3. severe loss of weight and 4. jaundice.

Serum amylase or diastase are uniformly elevated in acute pancreatitis in the first forty-eight hours. Serum lipase is elevated in acute pancreatitis and in about 40 per cent of the cases with carcinoma of the pancreas. Stool examination may show an increase in the unsplit fat and in the nitrogen content. In carcinoma of the pancreas duodenal drainage shows an absence of bile and the presence of blood and occasional tumor cells, while double tube intubation shows a decrease in pancreatic enzymes in carcinoma of the pancreas. Urinalysis, blood sugar determinations, and glucose tolerance tests will frequently show frank diabetes or impaired glucose metabolism in patients with pancreatic disease.

GLUCOSE METABOLISM IN LIVER DISEASE

H. R. Rossmiller, M.D.

Endogenous glucose is derived from the liver either from glycogen stores or fats and protein. The liver can manufacture glucose from the glycerol portion of the fat molecule and certain amino acids. These mechanisms are important in the main-molecule and certain amino acids. These mechanisms are unimportant in the maintenance of normal concentrations of blood sugar.

The proof of the central role of the liver in sugar metabolism is best demonstrated by hepatectomy which rapidly produces hypoglycemia. Acute necrosis of the liver may also produce hypoglycemia due to failure of both the glucose storage and manufacturing functions of this organ. In chronic parenchymal liver disease such as Laennec's cirrhosis hyperglycemia may be present, apparently due to failure of the glucose storage function at normal blood sugar levels.

The amount of stored glycogen in the liver, as shown by Whipple and Sperry in 1909 is important in the prevention of liver damage. Large stores of liver glycogen increases resistance to liver damage and the feeding of large amounts of dextrose in the presence of a damaged liver accelerates recovery. The factors which influence the amount of glycogen in the liver are therefore of considerable importance.

Diet, the source of exogenous glucose, alters the amount of glycogen contained in the liver cells. Starvation depletes the glycogen reserve of the liver. High fat diets produce a similar effect and at the same time will cause a great deal of fat to be deposited in the hepatic cells. Conversely a high carbohydrate diet favors glycogen storage in the liver. A high protein diet produces a similar effect apparently by increasing manufacture of glucose from the source.

Various secretions of the endocrine glands particularly adrenalin, insulin and anterior pituitary extracts alter the amount of glycogen in the liver. Diminution of hepatic glycogen occurs when the liver cells are damaged by such toxic agents as chloroform, arsenic and phosphorus. Hepatotoxic agents are thought to act first as an irritant to the glycogenolytic mechanism of the liver, i. e. increase glycogen formation and favor depletion of the store.

After ingestion of carbohydrate in normal persons the blood sugar level rises and as this occurs glycogenesis begins with the aid of optimum insulin secretions. However extra insulin does not influence the deposition of glycogen in the liver. This observation is of importance as it pertains to patients who have hyperglycemia due to liver disease and who have a normal insulin secreting mechanism. It does not seem likely that added insulin would prove helpful in increasing glycogen deposition in the liver.

It is desirable to increase the glycogen deposition in the liver not only in the treatment of liver disease but also in its prevention. However, the feeding of high carbohydrate diets to patients with chronic parenchymal liver disease, particularly Laennec's

cirrhosis, may result in hyperglycemia and glycosuria. This should not deter continuation of such treatment for it has been shown by Cori and Cori that the level of the blood sugar concentration is all important in determining the rate of glycogen deposition in the damaged liver.

DIABETIC COMA

*Edmund E. Beard, M.D.**

Diabetic coma is the most serious complication of diabetes mellitus, as it is almost invariably fatal if not adequately treated. Since the advent of insulin coma has become to a large extent avoidable and much more amenable to treatment.

Understanding of its pathogenesis has contributed greatly to improvement in prevention and treatment of coma. The outstanding events in its development are:

1. Decrease in insulin effect, such as in failure of the diabetic to take his insulin, or insensitivity to insulin as may occur in infections.
2. Decrease in utilization of carbohydrate. Combustion of fat is increased.
3. Increase in ketone production. These are the normal products of the catabolism of fatty acids, not in themselves pathologic, but as a consequence of "2," they accumulate at an enormous rate. As they are acid they must be excreted. To do this the body must sacrifice base.
4. Alkali reserve reduced.
5. Sodium is lost, excreted as no-ketone salt.
6. Water goes with sodium—dehydration occurs.
7. Eventually shift in Ph of the blood to the acid side.
8. In coma there is often a progressive decrease in effectiveness of insulin.

There is no entirely satisfactory definition of diabetic coma. Certainly no single function can serve as a diagnostic criterion. We must consider the concentration of acetones in urine (and blood), the degree of depletion of alkali reserve, the degree of dehydration, and the degree of consciousness. The appearance of acetone in the urine of the diabetic is a danger signal, and calls for treatment.

Precipitating factors of coma are: 1. acute infection, 2. omission of insulin, 3. vomiting and diarrhea, 4. prolonged lack of good control, 5. indiscretion in diet, 6. operations, 7. pregnancy, 8. thyro-toxicosis and other endocrine disturbances, 9. insensitivity to insulin.

The onset may be insiduous and variable. Increasing listlessness, loss of appetite, dryness of mouth, throat and tongue, polydipsia and polyuria are common. Symptoms of poorly controlled diabetes are followed by those more specific of acidosis: nausea, vomiting and diarrhea, pain in abdomen, drowsiness, air hunger and loss of consciousness.

The patient looks desperately ill. There is air-hunger (in extremis respirations may become rapid and shallow) and acetone odor on the breath and severe dehydration. The skin is cool and dry. Mucus membranes and tongue are dry. Eyeballs are soft. The temperature usually is low, even with infection. Blood pressure is low: the pulse rapid and soft.

Blood sugar is usually 400-800 mg./100 cc. More important is increase of acetone in urine and blood, which latter is the real index of danger from ketosis per se (it may increase while the carbon dioxide combining power of the blood is returned to normal by administration of alkali.) Carbon dioxide combining power is low, usually below 20 vols. per cent. The urine is of high specific gravity and contains sugar, acetone, albumen and casts. In the blood, cholesterol, fat, and non-protein nitrogen are in-

creased, sodium chloride is decreased. Red count hemoglobin and hematocrit are high. The white blood count is increased beyond the effect of hemoconcentration.

Infection should always be in mind because it is often present, may be not readily apparent, and is of high importance. Furuncles, gangrene, pneumonia, otitis media, and urinary infections especially should be sought, and should be treated on suspicion.

Two syndromes likely to be mistaken for diabetic coma are hypoglycemic coma and cerebral accident. In both the history is important, there will be no dehydration and there probably will be no acetone in the urine. If there is any doubt, intravenous glucose, *not* insulin, should be given.

The prognosis is good if the patient is young, only drowsy, if blood pressure is not low, if there is no complicating infection, if the carbon dioxide is low in amount. It is grave if the patient is over 40 years, if completely unconscious for over twelve hours, if the systolic blood pressure is under 50 mm. Hg., if severe infection is present, if there is anuria and severe nitrogen retention, if there is much cardiovascular disease, if the blood sugar is over 1000 mg./100 cc. and if treatment is not vigorous.

Preventive treatment includes elimination of acetone from the urine. Insulin should not be omitted when the patient cannot take food unless there is no acetone and the blood-sugar is low or the urine sugar free.

The treatment of coma includes: 1. Insulin, the specific. Initial dose will vary from 50 U in the mild to 200 U in the very severe cases, given half and half subcutaneously and intravenously (to guard against failure of absorption). Never rely on intravenous dosage alone. Follow-up doses are given every two to four hours in amounts varying with the rate of improvement. If there is no sign of improvement in four hours, high dosage must be maintained or increased, as in some cases insulin may be completely ineffective. Cases of recovery are reported after the use of over 5000 U in twenty-four hours.

Protamine insulin should never be used alone in the treatment of coma; it may be used in part. One must remember that there may be rapid increase in the effectiveness of insulin as improvement occurs. It is for this reason that we prefer to use protamine insulin in doses not to exceed 40-50 U as an initial dose.

2. Fluids. Normal saline given in amount needed to restore kidney function and eliminate dehydration. Figure usually about 5 per cent of body weight, 30-40 Gm. of sodium chloride.
3. Glucose. Given as 5 per cent solution with the saline as needed to prevent hypoglycemia. Almost never necessary in first few hours; it may operate to slow dehydration by maintaining high blood sugar and high diuresis; 100 Gm. or more in first 24 hours.
4. External warmth, using great care not to burn. Gastric lavage and enema, often recommended, can usually be omitted, or at least deferred.
5. Food. As soon as consciousness is regained. Valuable as a source of carbohydrate and of vitamins and minerals, perhaps potassium especially.
6. Alkali. Its only indication is severe hyperpnea with carbon dioxide combining power below 20 vols. per cent. The mere restoration of this level to normal confers no benefit. Ringer's solution or Lactate Ringer's solution may be used for this purpose and it has the advantage of containing some potassium, which offers protection against hypopotassemia, undoubtedly in some instances a complication of the treatment of diabetic coma, though we have not yet recognized it in any of our cases.

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(*To be concluded in the next issue*)