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Glucose tolerance tests as a measure of carbohydrate metabolism in the healthy elderly patient

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The prolongation of human life has been of interest from the beginning of time. Many articles are appearing in which questions pertaining to the aged are being discussed. The increase in life expectancy has been entirely due to the steady progress which has been made in the art and science of medicine in general and in preventive medicine in particular. Never before have there been so many old people. In a survey made by Boas (9), it was found that there now are six million more persons who are 65 years of age or older in the United States than there were in 1900, and it was estimated that in 1980 the total number of this age group in the population will be about 22 million. It is for this reason that the study of the problems of the aged patient (gerontology) presents such vast opportunities and demands for clinical investigation.

One of the interesting fields of such investigation concerns the changes in the function of the human liver in old age. Carbohydrate metabolism,

which is best studied by means of the glucose tolerance test, is very intimately related to this organ. It is with this thought in mind that the following work with the glucose tolerance test in the healthy elderly patient is being reviewed.

Specific studies of the pathological changes in the senile human liver have been made in recent years. Frischman (28) studied connective tissue in human livers of patients between the ages of 6 months and 80 years and concluded that there was no change in the relative amounts either of the collagenous or of the reticular connective tissue as compared with parenchyma in advancing age. Of the parenchyma itself, he found no decrease in cell size in old age. Other investigators (4) (100) in a study of livers in persons over 65 years of age found that this group showed a distinctly different picture from younger specimens. In almost every low power field were found aberrant nuclei, hypertrophied and irregular in shape. These nuclei often contained multiple nucleoli (15-20 in number). Intranuclear inclusions were very frequent. Infiltration, varying in extent, was found in 70 percent of the cases under study. Cytoplasmic changes were numerous and marked and

consisted of acute parenchymatous degeneration, fatty infiltration and fatty degeneration. These changes were not characteristic nor at all constant when comparing one senile liver to another, or one part of the tissue section to another. The nuclear changes however were characteristic. It was felt that the intranuclear inclusion bodies were due to metabolic disturbances attendant upon senescence of the organism rather than being virus in nature, because they were homogeneous rather than consisting of aggregates of smaller bodies. In the opinion of Meyer (76), cirrhosis of the liver is not found as a phenomenon of ageing. In a later work by Strassman and Krush (100) however, increased fibrous tissue formation with round cell infiltration was found to be predominant. In addition to the fibrous tissue formation, these authors found passive congestion, atrophy of the cells in the central parts of the lobules, increased lipofuscin and generally extensive fatty metamorphosis of liver cells. In rats, however, Lowry (66) found little or no change in the structure of the liver with senescence.

The probable causes of this fatty metamorphosis have been reviewed by numerous recent investigators,

many of whom have adopted the general belief that the metamorphosis is due to deficiencies in protective foods and vitamins. Among recent works on this subject, Drill and Loomis (22) and Freeman (27) have indicated the importance of Vitamin B Complex and especially Vitamin B_1 (thiamine chloride) in the prevention of fatty changes.

To assist in a more complete evaluation of the findings of the glucose tolerance tests, a brief review of some of the most significant literature concerning the physiological and biochemical phenomena of carbohydrate metabolism has been made.

Carbohydrate Digestion and Absorption

Although the main function of the saliva in man is to moisten the food to facilitate swallowing, it also contains an enzyme, ptyalin, which acts upon boiled starch breaking it down by hydrolysis in successive stages into dextrins of various sized molecules and finally into maltose. Although the food usually spends only a short time in the mouth, thus allowing only a small amount of hydrolysis to occur here, the process is continued in the stomach until it is inhibited by the gastric acidity. This often takes a considerable time and a large

portion of the ingested starch may be hydrolyzed by this enzyme. The simpler carbohydrates are not attacked by ptyalin. Unboiled starch is acted on only very slowly by either ptyalin or the diastatic enzymes of the pancreatic juice, and if large amounts of it are ingested, a considerable portion will ultimately appear unchanged in the feces.

Even though the acidity of the gastric juice inhibits or inactivates ptyalin, it aids carbohydrate digestion by commencing the hydrolysis of the disaccharides, particularly sucrose. It was thought at one time that invertase, a special enzyme of the gastric juice, was necessary for this inversion of cane sugar but this idea has been shown incorrect as inulin, a polysaccharide yielding fructose on hydrolysis, is also attacked by gastric juice and can serve as a source of dietary carbohydrate.

The most important digestive fluids affecting carbohydrates are found in the pancreas and small intestine. Amylase, a pancreatic enzyme, completes the hydrolysis of starch to maltose. The intestinal enzymes maltase, sucrase and lactase cause completion of the hydrolysis of the disaccharides maltose, sucrose, and lactose respectively. These are intra-

cellular enzymes which act on the disaccharides, converting them to their constituent hexoses after their passage into the cells of the intestinal mucosa. The old idea that the three enzymes were secreted into the succus entericus is probably attributable to the presence of cellular elements in the specimens of juice examined. On the completion of intestinal digestion all of the major disaccharides and polysaccharides of the diet have been converted into hexoses, chiefly glucose, but also fructose and galactose, in which form they are directly assimilable.

Extensive studies of the absorption of carbohydrate from the alimentary canal have been made by Cori (17) (18). Known amounts of sugar were fed by stomach tube to experimental animals and the total amount of sugar absorbed obtained by subtracting the amount of sugar remaining in the stomach after the test period. The effects of bacterial action were studied and found to be insignificant. The amount of sugar absorbed from hour to hour remained quite constant although the amount of sugar present in the intestine diminished all of the time. It was concluded that the rate of absorption was,

within wide limits, independent of the amount of sugar present in the intestinal tract because it was found that large amounts of sugar in the intestine merely prolonged the period of absorption and did not result in a more rapid absorption.

Glucose, galactose and fructose are absorbed more rapidly than sugars which do not occur frequently or in quantity in our diets. This selective absorption of the various sugars was found to be characteristic of all mammals. It was also found in experimental animals that the highly selective action of the intestinal mucosa on sugars is not a property common to all absorbing membranes. When sugars were absorbed from the peritoneal cavity it was found that the rate of absorption decreased with decreased concentration of the sugars in the peritoneal cavity. The finding that when two substances were fed simultaneously the rate of absorption of each was reduced, has been termed mutual inhibition of absorption. Cori believed the explaination lay in the postulation that only a limited number of sugar molecules could pass through the intestinal epithelium per unit of time. For the same reason it was found impossible to increase the rate of absorption of sugar no matter

how much sugar was fed. There was no indication that the emptying of the stomach was a limiting factor. The relative rates of absorption of the various sugars were found to be directly proportional to the rates of actions of the specific enzymes entering into their hydrolysis. The rate of absorption was also found closely related to the general condition of the animal as starvation was shown to reduce markedly the rate of absorption. Other authors (77) have shown a direct relationship between vitamin deficiencies and glucose absorption, but Cori believes the vitamin deficiency to be only a secondary factor and that the initial cause is the increased evacuation time of the stomach seen in these conditions.

The actual mechanism of absorption of carbohydrates in the form of hexoses is as yet not clearly understood. It was the opinion of earlier workers that in transit through the intestinal wall glucose was converted into some other substance, possibly glycogen or some other compound. Any transformation of this kind would assist absorption by increasing the diffusion gradient. There has been little experimental work to support this idea however.

Another idea which is more firmly founded on

experimental work is that phosphorylation of the hexoses occurs in the intestinal wall (23). It has been well established that the intermediary metabolism of hexoses in other tissues is intimately linked with reactions involving phosphorylations and dephosphorylations of organic phosphates. Further suggestive evidence is found in the fact that iodoacetic acid and phloridzin (which are known to inhibit carbohydrate metabolism in muscle by interfering with phosphorylation) inhibit glucose absorption. Iodoacetic acid exerts its effects on the essential enzymes containing sulfhydryl groups and phloridzin on enzymes that initiate the phosphorylation of glycogen and glucose.

Other authors (8) however, believe that the increased amount of esterified phosphate in the intestinal mucosa may be related to metabolism rather than absorption or may be due to slow dephosphorylation. Also the slow absorption of glucose from the small intestine after hypophysectomy or adrenalectomy may suggest that inanition rather than the loss of any specific adrenal phosphorylating factor may be very important in this question, as the administration of sodium salts restores the rate of glucose absorption

in adrenalectomized animals. Russell (92) also found diminished glucose absorption rates in hypophysectomized rats but believed this due to the concomitant thyroid atrophy, and has shown that the absorption may be returned to normal by thyroxin injections. This work by Russell has been substantiated by Verzar and McDougall (105), but these authors believe in the now disproved theory that adrenalectomy reduces the absorption rate of pentoses due to adrenal cortical insufficiency which in turn caused deficiency of cortical hormone necessary for phosphorylation processes.

Regulation of the Blood Glucose Level

That the liver is the source of blood sugar in the fasting animal was first demonstrated by Claude Bernard in 1853. Since that time many improvements in technique have made the use of experimental animals very important in the development of our knowledge on this subject. The extensive work of Mann and his collaborators (11) finally established the liver as the prime factor for the maintenance of the normal blood sugar level, and the role of muscles in the supply of sugar to the blood was shown to be insignificant.

The fact that sugar is supplied to the blood by the liver when it is not being received from the gastro-intestinal tract or other exogenous sources is well established. Under experimental conditions, in the hepatectomized animal, there is rapid, profound, and fatal hypoglycemia if not alleviated by continuous administration of relatively large amounts of glucose. Soskin (95) postulated that the dynamic balance between the rate at which sugar is entering the bloodstream from the liver and from any exogenous source, and the rate at which it is being removed from the blood by the tissues of the body represents the blood sugar level. Thus it is easy to see that a rise in the blood sugar level may be due either to an increased rate of supply or to a decreased rate of utilization, or both. The converse applies to a lowering of the blood sugar level. It is not possible to tell which of these factors is responsible for the change in the blood sugar level unless one factor is controlled or eliminated while the other is observed.

Since the blood sugar of mammals remains normally in the neighborhood of 0.1 per cent, there must exist a regulatory mechanism which is set in motion

whenever the blood sugar ranges much below or above this figure. It is now quite generally accepted that a rise in the blood sugar elicits a secretion of insulin and that a fall in blood sugar below a certain level is followed by a discharge of epinephrine. The mechanism of blood sugar regulation is therefore intimately connected with the action of these two hormones on blood sugar production and utilization. The endocrine mechanisms related to the control of the blood sugar level are very complex and will be discussed in such a manner as to demonstrate the relationship of the liver and the endocrine glands involved.

Of first consideration in the subject of regulation of the blood sugar is the homeostatic mechanism in the liver itself. The relative constancy of the blood sugar level in the normal animal at all times indicates the existence of a regulating mechanism. Claude Bernard was keenly aware of the dynamic balance involved in carbohydrate metabolism and stated that the blood sugar level represented a precise equilibrium between the rates of sugar formation in the liver and sugar utilization in the tissues (31). The characteristic rise and fall of the blood sugar

following the administration of dextrose to normal animals represents a rapid and accurate re-adjustment of the blood sugar level, and offers a simple and reproducible test of the regulating mechanisms. The fact that the liver is the only organ that possesses a store of glycogen that can be rapidly converted into glucose and is capable of forming glucose from non-carbohydrate sources in quantities sufficient for the body needs makes it the predominant organ in the regulation of blood sugar concentrations.

Much experimental work has been done on the homeostatic mechanism by Soskin (95) by the use of depancreatized and hepatectomized dogs. He showed that in the presence of sufficient insulin, but not necessarily an extra secretion from the pancreas, the normal liver, as one of its responses to administered dextrose, decreases the output of blood sugar which it has been previously supplying from its own resources. In the normal animal, a rise in the blood sugar level causes the liver to respond by diminishing its output of sugar to the blood. The stimulus which elicits the hepatic inhibitory response is the blood sugar itself; and the threshold

of stimulation depends largely upon the endocrine balance, and coincides with the level of blood sugar which is normally maintained.

In earlier reviews on the subject of endocrine control of carbohydrate metabolism, first place in the discussion would have been given to the influence of the Islets of Langerhans. It has been found however, that this endocrine organ is only one member of the glandular system whose secretions participate in this control. The essential role played by the internal secretion of the pancreas has been recognized since the discovery of Minkowski in 1893 that total pancreatectomy was followed by severe disturbances in carbohydrate metabolism. Soskin (95) later advanced the knowledge in this field by finding that the secretions of the pancreas and the anterior hypophysis were closely related, and that in a hypophysectomized-depancreatized animal, life could be maintained in the absence of insulin. In the intact animal a certain amount of insulin must be constantly secreted to balance the equal and opposite influence of the anterior hypophysis and other factors, in order that the regulation may occur at physiologically normal blood sugar levels.

The secretion of additional insulin is not essential to the primary hepatic regulation but there is considerable evidence to suggest that extra insulin is ordinarily secreted as a result of hyperglycemia. The exact purposes served by this additional insulin are not entirely clear. It therefore seems fair to conclude that, while the secretion of extra insulin is not essential to the intrinsic hepatic mechanism, it acts under normal physiological conditions as a factor of safety in increasing the efficiency of this type of regulation. Another effect of the increased supply of insulin is to decrease carbohydrate storage in the liver of the normal person, rather than to increase it (19).

The characteristic changes observed in the metabolism of the totally depancreatized dog as reported in the literature have been reviewed by Duncan (23) and are as follows:

(a) There is pronounced glucosuria and hyperglycemia which does not disappear on fasting.

(b) There is disappearance of liver glycogen with some reduction of muscle glycogen, although the latter is maintained to a surprising degree.

(c) The ingestion of glucose is followed by its

almost quantitative excretion in the urine.

(d) The respiratory quotient falls to the fat level of 0.71 and is not elevated by glucose ingestion.

(e) In fasting animals or those on a meat diet, there is established a relative constancy between the nitrogen and glucose excreted in the urine. This G/N ratio is approximately three and indicates that a constant proportion of the protein derived from the diet or tissues is converted into glucose. Of equal importance is the increased level of nitrogen excretion in fasting animals which implies that the rate of tissue protein breakdown has been accelerated.

(f) Marked acetonuria develops, which is probably due to the accelerated catabolism of fat.

(g) In totally depancreatized dogs and cats severe dehydration, acidosis, coma and finally death ensue.

The anterior hypophysis is also very important in the proper regulation of carbohydrate metabolism. It acts by its trophic effect on the thyroid and adrenal cortex and by some principle that apparently acts directly on the tissues. The secretions of the anterior lobe of the pituitary gland oppose the action of insulin in the regulation of the blood

sugar. This has been termed the glycotropic or anti-insulin action of the anterior pituitary. It effects the threshold of regulation of the homeostatic mechanism, the rate of gluconeogenesis and through its adreno-cortico-tropic factor causes storage of large amounts of glycogen in the liver. Russell (91) has made a comprehensive review of the effects of the anterior pituitary on carbohydrate metabolism. The main effects that have been observed are as follows:

(a) Control Over Glucose Absorption-- A lack of pituitary hormone decreases the rate of absorption from the intestine, but this effect may be counter-balanced by the administration of thyroxin (92).

(b) Carbohydrate Levels-- A deficiency of the anterior pituitary hormone in a fasting animal causes depletion of the carbohydrate levels of the blood, liver and muscles and causes marked elevation of the respiratory quotient. This action is believed due to the glycostatic effects of the anterior pituitary. This finding is explained on the basis that these animals are either failing to produce sufficient carbohydrate for their needs from non-carbohydrate sources (hepatic gluconeogenesis) or

else are oxidizing their carbohydrate stores at an abnormally rapid rate. It is further believed that an anterior pituitary factor is actively concerned either with glucose production from noncarbohydrate source, an inhibiting effect on glucose utilization or both glucose production and utilization.

Soskin (95) found that removal of the hypophysis from the normal well fed dog caused lower blood sugar levels and believed this due to the effect in the threshold of the homeostatic mechanism. He supported the idea of reduced gluconeogenesis in the absence of hypophyseal secretions in these animals by showing that the fasting hypophysectomized dog showed severe hypoglycemia causing death. The decreased nitrogen excretion in these hypophysectomized dogs is believed by Soskin to be due to the decreased gluconeogenesis from protein.

(c) Storage and Oxidation-- Less glycogen is stored in the liver of the hypophysectomized animals and a larger percentage is oxidized. In normal animals, an increase in this hormone decreases the amount of glucose oxidized and increases muscle glycogen storage. The ability of the anterior pituitary extract to promote muscle glycogen storage

or to prevent its loss in hypophysectomized animals has been termed the "glycostatic effect" by Soskin (95).

(d) Insulin Sensitivity-- Insulin increases glucose utilization and rapidly reduces the carbohydrate levels of the hypophysectomized animal to the danger point. In such animals, the sensitivity of insulin is therefore very much increased.

(e) The Diabetogenic Action of the Anterior Pituitary-- An excess amount of the extract of the anterior pituitary causes a hyperglycemia, glycosuria and acetonuria. This diabetogenic action is due in a large part to destruction of the Islets of Langerhans with decreased anti-diabetic hormone, insulin, but may also be due to nullifying the effect of insulin and decreasing the utilization of glucose.

(f) The anterior pituitary gland also affects carbohydrate metabolism through the thyrotropic and perhaps also through the gonadotropic substances. Removal of the adrenal cortex, thyroid, or the gonads produces histological changes in the anterior pituitary but the functional significance of these is not as yet clear.

It has been suspected for years that the thyroid

gland has been related to the metabolism of carbohydrate but its exact effect is unknown at this time. The altering of the metabolic rate is probably intimately related to carbohydrate metabolism. The aggravation of diabetes in man by hyperthyroidism and its amelioration by removal of the thyroid suggests such a relationship. The administration of thyroxin causes increased tissue protein catabolism, increased protein gluconeogenesis in the liver, increased rate of oxidation of carbohydrate in the tissues, a reduction in liver glycogen and an increased rate of intestinal absorption (8) (23) but there is no immediate effect of thyroxin on the blood sugar (8) (95). Continued increase in thyroxin causes decreased liver, muscle and heart glycogen (8) and extreme susceptibility to insulin with resistance to adrenalin.

The exact relationship of the adrenal cortex to carbohydrate metabolism is still unknown. There is still some question whether the adrenal cortex influences carbohydrate metabolism primarily or whether its effects are secondary to its control of electrolyte balance. Observations in animals by Soskin and his group and others have shown the following significant findings:

(1) That animals suffer depletion of their carbohydrate levels in liver, muscle and body fluids. This effect can be corrected by administration of glucose and cortical hormone.

(2) Another finding demonstrated is that the phloridzinized-adrenalectomized rats excrete less glucose and nitrogen than intact animals.

(3) On exposure to low oxygen pressures fasting rats show an increase in their liver glycogen while adrenalectomized rats do not.

(4) Adrenalectomy alleviates pancreatic diabetes.

(5) Injection of cortical hormone causes increased liver glycogen and mild hyperglycemia.

(6) Cortical hormone will cause exacerbation of mild diabetes of hypophysectomized-depancreatized and of adrenalectomized-depancreatized animals.

(7) The rapid depletion of carbohydrate levels of fasting hypophysectomized rats may be prevented by the injection of the cortical hormone.

(8) Cortical extract produces glycosuria by stimulating gluconeogenesis from protein and by interfering with glucose oxidation.

(9) Disturbance of sodium and potassium metabolism causes delayed absorption of sugar and failure to

store glycogen.

Although these definite effects are seen in animals and are probably applicable to man, other effects are not known. It is realized, however, that this portion of the adrenal is an important gland in the system of carbohydrate metabolism regulators.

The adrenal medulla which secretes epinephrine is also related to carbohydrate metabolism. Epinephrine causes hyperglycemia and glucosuria due to the effect of driving the organism's production of glucose beyond normal bounds of power of assimilation. Its action is due in a large part on the presence of preformed liver glycogen. Under the influence of this hormone the liver glycogen is rapidly converted into glucose and the blood glucose level may in a few minutes be doubled or trebled if an adequate supply of liver glycogen is present. It acts the same as with sympathetic stimulation and fits into the emergency mechanism of the body. Cori and Cori (19) found that epinephrine produces a hyperglycemia even in fasted animals until their liver glycogen was less than 0.5 per cent. The hyperglycemia lasted several hours and could not be explained by such a low initial liver glycogen level. They found that

the liver glycogen gradually increases during the period of action but that the muscle glycogen decreases. The hormone evidently increases the rate of glycogen breakdown both in the liver and muscle, liberating it in the former as glucose and in the latter as lactic acid. The lactic acid derived from the muscle glycogen is transformed by the liver into glycogen which is again liberated as glucose, thus maintaining the hyperglycemia.

After extensive investigations by many competent students of the subject of hormonal control of carbohydrate metabolism, it has been determined that the posterior pituitary is not related to glucose metabolism.

Finally, it is necessary to mention the parts played by the central and autonomic nervous systems. Claude Bernard paved the way for the investigation of the influence of the nervous system when he punctured the floor of the fourth ventricle in an unanesthetized animal and obtained a resultant prolonged glucosuria. That lesions in the hypothalamic region may cause glucosuria has been appreciated for some time. The exact mechanism involved here however remains unknown. It has been suggested by

some authors that these lesions might interfere with the absorption of the pituitary hormones or stimulate or destroy the nerve fibers going to the gland. The more accepted idea is that lesions of the brain or brainstem involving the pathways which carry glycogenolytic impulses to the liver or the tracts which supply the adrenals, pancreas or pituitary cause marked disturbances in carbohydrate metabolism. It has been determined that stimulation of the posterior hypothalamic nuclei produces a hyperglycemia through the sympathico-adrenaline mechanism. Lesions of the paraventricular nuclei cause increased sensitivity to insulin and a prolonged hypoglycemia. Lesions of the tuber cinereum in the lateral hypothalamic area act in the same way as hypophysectomy in ameliorating the diabetes produced by pancreatectomy (8).

Formation of the Blood Sugar

Blood sugar is formed in the liver by two processes. The first, gluconeogenesis, is the production of glucose and glycogen from non-glucose substances. The second, glycogenolysis, is the splitting of glycogen to form glucose.

In early studies of gluconeogenesis Soskin (95)

found it advantageous to use diabetic organisms because with these animals it was thought that the extra-excretion of sugar in the urine following the administration of a known amount of foodstuff could be taken as the measure of the extent to which the foodstuff had given rise to blood sugar. The rationale of this method was based upon evidence that the diabetic organism could not store much carbohydrate, and upon the assumption that the newly-formed sugar could not be utilized but was rather excreted quantitatively into the urine. However Soskin and others later found that the diabetic organism can and does utilize large amounts of blood sugar, thus necessitating careful interpretation.

The subject of the non-carbohydrate precursors of the blood sugar, especially protein, was first studied by Mering and Minkowski (95). They used depancreatized dogs and concluded that these animals had lost the power to utilize carbohydrate because they exhibited extensive glycosuria and especially because the amount of sugar in the urine was more or less quantitatively equal to the amount of sugar ingested. They also found that the amount of glucose excreted in the urine bore a fairly constant relation-

ship, which was not affected by varying the amount of protein in the diet, was named the D:N ratio. Minkowski interpreted this ratio to mean that protein was the sole source of the excreted sugar, and that a constant proportion of the protein was being converted into sugar. This interpretation has been criticized by many workers who have failed to obtain the same results. Similar studies may be done with the phlorizinized animal, but the D:N ratio of phlorhizin-treated animals cannot signify that no sugar is being utilized, or that the sugar which is excreted represents either the partial or total amount which is being formed from protein alone. The chemistry of the process by which protein or amino acids are changed to glucose is quite complex and will not be discussed here.

Gluconeogenesis from fatty acids also may be an important part of the carbohydrate cycle. This mechanism has been confirmed by demonstration in vitro that sugar may be formed from acetoacetic acid by kidney slices. The chief constituents of this reaction are butyric acid, acetoacetic acid, succinic acid and hydroxybutyric acid. End products are lactic acid and hexose.

The liver is able to convert a large variety of substances into glucose and in most cases this involves intermediary glycogen formation-- glycogenesis. The final step in the process of sugar formation in the liver consists in the enzymatic hydrolysis of glycogen-- glycogenolysis. This process is inhibited by the presence of insulin and accelerated by epinephrine. The mechanism of glycogenolysis is now quite satisfactorily worked out. The presence of both glycogen and glycogenase in the same cell makes it necessary to assume that a large part of the enzyme is unable to act on the substrate, otherwise the glycogen would quickly disappear from the liver. Twelve enzymatic reactions are involved in the anaerobic conversions of glycogen to lactic acid. The phosphorylation of glycogen and of glucose has been proved to be the introduction to a long series of changes by which these products are transformed through various phosphate esters to pyruvic or lactic acid. Glycogen, after phosphorylation, breaks down to glucose-1-phosphate which is then converted to glucose-6-phosphate and then to glucose.

With this brief review of the essentials of carbohydrate metabolism in mind, it will now be

possible to discuss in full the glucose tolerance test and the problems that arise in connection with it in relationship to the healthy elderly patient.

The Glucose Tolerance Test

The prevailing concepts of the mechanism of the dextrose tolerance curve were reviewed by Soskin, Allweiss and Cohn (96). The administration of dextrose normally stimulates the pancreas to an increased secretion of insulin. It is this increased amount of insulin in the circulation that accounts for the normal dextrose tolerance curve by bringing into play increased storage and oxidation phenomena. The abnormal tolerance curve in diabetes mellitus and in depancreatized animals is due to the lack of pancreatic response to the administration of sugar. The "diabetic" type curve obtained in starvation is the result of the lack of response from a normal pancreas due to the lack of carbohydrate per se rather than lack of nutrition.

Normal reactions to the administration of dextrose were obtained in totally depancreatized animals by Soskin. This was found to be incompatible with the prevailing views given by other authors and reviewed above. This vitiates the importance of the

hypothesis of La Barre (57) that hyperglycemia stimulates secretion of insulin from the pancreas by acting upon a center in the thalamic region of the central nervous system, the stimulation then being transmitted through the parasympathetic system. The results obtained by Soskin were more in accord with the works of Quigley (85), Gayet and Guillaumie (29) and of Houssay (47) (48) which showed that the blood sugar level could be efficiently regulated in animals in which the pancreas had been freed from central vagus control and in animals which possessed only pancreas grafts. These results are contrary to the hypothesis of Sweeney (101) who has postulated an intermediate hormone which is secreted during hyperglycemia and acts upon the pancreas to stimulate production of insulin. Also, the results were not incompatible with the hypothesis of Himsworth (40) (42) who believed that hyperglycemia is followed by the liberation from the liver of "insulin-kinase" which then activates the previously inert insulin which has already been secreted into the blood stream. Himsworth's conclusions were based on work in which the arterial and venous blood sugar determinations differed. Others however, have shown that the

arterial venous differences can be used only in special cases and under restricted conditions (96). Campbell and Macleod (14) after basing their work on that of Allan (1) suggested that insulin may act according to laws governing enzyme action and therefore the characteristic normal tolerance could be explained as being due to increased activity of insulin already present in the circulation upon the greater amount of substrate which appears. These hypotheses however were later disproved by Houssay (49) who showed the importance of the hypophysis in carbohydrate metabolism.

Stimulated by Houssay's work, Soskin (96) was able to obtain normal dextrose tolerance curves in completely hypophysectomized-depancreatized dogs which had received no insulin for weeks. This removed the necessity of accounting for the normal dextrose tolerance curve by assumption of the insulin activating mechanism or of an increased glucose equivalent of this hormone. It was determined that there was no appreciable storage of insulin in the tissues.

The presence of a normal liver is essential for the normal dextrose tolerance curve. When the liver

is absent, the intact pancreas cannot produce the normal response. These results could not be reconciled by Soskin (96) with prevalent ideas that the storage and utilization of carbohydrates are the chief factors concerned in the normal dextrose tolerance curve. It had been shown by Bollman (11) that the liver is the sole source of blood sugar in the fasting organism and Soskin (93) also found this to be true. The blood sugar level in this condition therefore represents a balance between the sugar leaving the blood and sugar entering the blood from the liver. The fact that a fairly constant blood sugar level is usually maintained in the fasting state indicated that these processes ordinarily continued at relatively constant and mutually inter-dependent rates. The fall in blood sugar curve may be due to an increased loss of sugar from the blood to the tissues or to decreased entry of sugar into the blood from the liver or both. Soskin believes decreased output of sugar from the liver is the most important though not the only factor in determining the characteristic fall in the blood sugar curve after dextrose administration.

In other experiments Soskin found that the

influence of previous sugar administration on the subsequent curve can be demonstrated in the absence of the pancreas and is not due to the increased responsiveness of this organ. In the presence of sufficient insulin the normal liver decreases the output of blood sugar which it has been supplying from its own resources and a response is seen to the administration of dextrose.

Since it is unnecessary to assume a mobilization of insulin from the pancreas in order to account for the normal glucose tolerance test curve, the occurrence of the normal tolerance curve cannot be used as presumptive evidence that such a mechanism exists. Soskin (96) found a rational explanation for the "diabetic" type of tolerance curve, and associated low respiratory quotient, obtained in starvation and during dietary regimen of protein and fat, despite the presence of a normal pancreas. Although the liver is a major factor in determining the dextrose tolerance curve, its normal response to oral sugar administration is due to the influence of a suitable endocrine balance. This balance consists of opposing influences of the pancreas and hypophysis (which is inter-related with the thyroid

and adrenal glands). When these glands are exerting their normal and proportionate influences upon the liver, a blood sugar level slightly above the range of normal is an adequate stimulus to the liver for readjustment of the blood sugar towards the normal range. A sudden influx of exogenous sugar produces a reaction recognized as the normal dextrose tolerance curve. When endocrine relationships are disturbed, the blood sugar level may far exceed the normal range before it becomes an adequate stimulus for the liver readjustment. In experimental animals endocrine relationships may be upset and excessive gluconeogenesis results from removal of the pancreas. In the human diabetic the same may ensue because of inadequacy of the Islands of Langerhans or excessive activity of the hypophysis. The increased gluconeogenesis must also occur (providing no assumption of decreased utilization of sugar is made) in the fasting state and during a diet composed only of protein and fat. Under these conditions, endocrine balance is maintained. Hence, with the repeated glucose tolerance tests the results are successively more and more normal. That liver in starvation responds with decreasing production and outpouring

of sugars into the blood. The relation of excessive gluconeogenesis to low respiratory quotient and the coincidental decrease of gluconeogenesis with an increased respiratory quotient may also be explained by this means.

Glucose given by mouth in the normal animal causes a rise of blood sugar within two to three minutes indicating the rapidity with which solutions pass through the stomach to the duodenum. Large amounts of sugar cause alimentary hyperglycemia and glycosuria. Moderate amounts of sugar give transient rises in the blood sugar and rapid return to normal levels. Factors determining the shape of the glucose tolerance curve in the oral test are the rapidity of absorption, the extent of the storage and utilization of glucose by the tissues and the rate of discharge of sugar from the liver. The first may be eliminated by using the intravenous injection of the sugar. The reaction of the tissues and liver to the intravenous glucose may be direct or indirect. When the blood sugar rises, the liver may discharge less sugar (96). The hyperglycemia may affect the liver and other tissues indirectly by increasing the insulin output and perhaps other endocrine adjust-

ments. The insulin liberated increases the oxidation and storage of the glucose and decreases gluconeogenesis. An abnormal curve may indicate inability of the liver or pancreas or both to perform their normal functions. It might be due also to defective oxidation and storage in the muscles. "An abnormal glucose tolerance curve does not necessarily indicate a deficiency of available insulin." (8).

Himsworth (42) found that there was diminished glucose tolerance and impaired sensitivity to insulin after high fat diets but that this was not associated with a pH change of the blood to the acid side, and likewise the increased tolerance after a carbohydrate diet was not related to the change of pH to the alkaline side.

In answer to the question: "Why, in the healthy person, does the hyperglycemia pass off and the blood sugar curve return to its normal original level at a time when absorption of the glucose from the alimentary canal is still proceeding?", it was the opinion of Mac Lean and de Wesselow (70) that the sudden intervention of the storage mechanism which abstracts sugar from the blood was more active than the process in which the sugar enters the blood.

It has been shown by Macleod and Pearce (71) that the existing glycogen content of the liver does not demonstrably influence the rate with which the liver removes dextrose from the blood of the portal vein. It has been recognized that the capacity of the liver to store glycogen is inadequate to account for all of the carbohydrate that is assimilated and it is believed that the excess is carried to the muscles and deposited there as glycogen. The remainder is either oxidized or more slowly converted into fat. Therefore, it should be expected that the power of the liver to store sugar as glycogen would be more marked when the organ is empty than full. However, the rate at which the liver converts sugar to glycogen will be the same.

The oral glucose tolerance test has been widely used for many years to determine the effectiveness of the mechanism of carbohydrate metabolism in the body. One of the earliest examinations of the responses of the human organism to the administration of glucose orally was made by Worm-Muller in 1884 (90). He showed the presence of glycosuria after the ingestion of fifty grams of glucose. Hofmeister initiated the terms "assimilation limit" and "toler-

ance". The former was defined as the highest dose of sugar an individual could take before showing glycosuria and the latter to mean the dose upon which a small increase will give glycosuria. He found the assimilation limit for a given animal was constant but for different animals this varied greatly. In 1917, Sansum and Wilder pointed out that the assimilation limit determinations were for many years freely interpreted as limits of tolerance (90).

The first observations on the blood sugar levels at intervals after ingestion of the test dose were made in 1913 by Bang (5) (90). In the same year Jacobsen (50) described a glucose tolerance test based on a blood sugar curve after ingestion of glucose. In this test a single dose of fifty to one hundred grams of glucose was given after a fast of from twelve to sixteen hours. He was able to differentiate the following three types of curves: (1) the "normal" curve, which in venous blood shows a peak below 0.17 percent and falls to the fasting level within two hours, and in capillary blood shows a peak below 0.20 percent and falls below 0.12 percent in two and one-half hours; (2) the "diabetic" curve which attains a peak above 0.17

percent in venous or 0.20 percent in capillary blood and is above 0.12 percent in two hours and two and one-half hours respectively and (3) the "borderline" curve which shows either a high peak or a delayed fall.

Widespread use of the glucose tolerance test in English speaking countries dates from Maclean's method of estimation of blood sugar which appeared in 1921 (70) (90). Mosenthal initiated the idea of weighing patients and giving of a definite amount of sugar per kilogram of body weight, but he later decided that this procedure was not always necessary because in fat people the increase in weight is not in muscle or glandular tissue which take part in carbohydrate metabolism but in fat which is relatively inactive in carbohydrate metabolism (78).

In a review of the literature concerning the oral glucose tolerance test, John (52) in 1923 emphasized the following points in the study of the glucose tolerance: (1) a large series of normals must be carefully chosen; (2) agreement in the test substance and dosage is essential; (3) a minimum fasting interval must be established; (4) consistent use of whole blood must be insisted upon; (5) constant

chemical technique is necessary; (6) the same technicians should run all tests used in published series and (7) particular attention should be paid to psychic hyperglycemia. Prior to the publication of John's article, much work was being done with the glucose tolerance test but due to poor standards practiced at that time, the test was still of no great value.

In another study by Hale-White and Payne (37), the important factors causing variation of the oral tests were discussed. In this study tests were given to healthy persons over sixty years of age. The dose of fifty grams of dextrose in one hundred cubic centimeters of tap water was given by mouth. The authors found the psychological element to be important, i. e., excitement, pain and apprehension caused a rise of the blood sugar in some cases. Ross found this rise to be as high as fifty milligrams percent at times (90). Hale-White and Payne (37) also found the rate of emptying of the stomach to be important. At the time of publication of their article in 1925 there was much controversy over the above points and some authors were beginning to use the intravenous glucose tolerance test in order

to avoid error from these sources. Ross (90) also found that the diet preceding the test was very important showing that a previous high carbohydrate diet consistently gave a lower glucose tolerance curve. These authors concluded (1) that in every oral glucose curve the descent has begun while there is still a fair quantity of sugar in the stomach, (2) that a sudden gush of sugar into the duodenum causes a rapid rise in the blood sugar curve, (3) that the stomach still contains some sugar even though the blood sugar has returned to normal, (4) that the rate of emptying of the stomach has but little effect on the associated curve but has considerable control over the time and rate of fall and (5) that nausea may have some effect on a blood sugar curve by causing the cessation of the intestinal peristaltic movements and in this way cause the slowing of absorption.

Horvath (46) came to the conclusion in 1947 that there still has been no general agreement either as to the method employed in the test or as to the measuring of results, which he has shown to be exceedingly variable. He believes that because the glucose tolerance test is the simplest procedure

available for the studying of the integrity of the entire mechanism of progressive carbohydrate metabolism from ingestion through absorption, storage, availability and oxidation that still further work should be done. Its extensive use during many years is evidence that it is fulfilling a need.

The approved schedule for the routine one hour, one dose glucose tolerance test is at this time quite standardized. Breakfast is omitted and the test conducted after fasting overnight. Urine and blood samples are taken prior to the test and sugar determinations made. Immediately thereafter 1.75 grams of glucose per kilogram body weight dissolved in five hundred cubic centimeters of water is given by mouth. It is advisable to flavor this with lemon and cool with ice to make it more palatable. One hour after the administration of the glucose a specimen of blood and urine is taken and this is repeated at hour intervals until a total of four specimens has been taken. The blood samples are then treated by the Folin-Wu technique to obtain a blood filtrate and a quantitative blood sugar determination made. This is then plotted on a graph to show the glucose tolerance curve. The

urine is examined by the Fehling-Benedict method and both qualitative and quantitative examinations may be made (56).

Hale-White and Payne (37) following their work in 1925 pointed out that all tests should be done at the same period of the day to overcome the problem of diurnal variations.

The dosage of the test varied considerably. American investigators use 1.75 grams per kilogram body weight; others use one hundred grams dissolved in varying amounts of water; in England fifty grams is usually given and in Scandinavian work one gram per kilogram body weight has been given. According to Maclean and de Wesselow (70) a dose above twenty-five grams given to a normal person does not cause a rise in the blood sugar greater than that caused by only twenty-five grams but merely delays the return of the curve to normal. Hale-White and Payne (37) find a higher rise with a large dose. Some authors believe that one hundred grams in one dose is harmful to the normal individual (34) (13) (51). Gray (34) found that the glucose tolerance curve varies with individuals and with the size of the dose of glucose. Larger doses are characterized

by a later peak.

The possibility of alterations in the curve through variations in absorption has been considered by many workers, but usually has been perfunctorily dismissed. The problem is a difficult one in man because the rate of absorption of glucose from the intestinal tract is difficult to determine directly (77). Groen (36) showed by use of the Miller-Abbot tube in the intestine of normal subjects that the amount of glucose absorbed from concentrated solutions under standard conditions is constant. Above ten percent concentration the amount of glucose absorbed was believed to be independent of the concentration of the solution introduced. This was compatible with Cori's Law (17). Normal absorptive values were found by Groen to vary under standard conditions from seven to nine grams of glucose (average of 7.77 grams). The age, sex and weight were not found to influence this figure. Also it was found that changes in the diet of relatively short duration did not affect the absorption rate.

Beeler (6) believed that for best absorption a solution not stronger than twenty percent strength should be used. He believed that this should be

limited to a volume of five hundred cubic centimeters. He found that twenty-two to sixty-eight percent of the dextrose given by mouth by this plan can be recovered by washing the stomach one hour after administration. It was believed by Ross (90) that solutions of a concentration of over twenty-five percent may produce nausea and erratic curves. He proposed the use of a twenty percent solution in water with some flavoring added. He found that saline should not be used as it interferes with absorption of the solution.

The question of the source of the blood and its method of withdrawal has also caused differences of opinion. Hale-White and Payne showed that the sugar control of the venous blood after ingestion of glucose is often less than that of the capillary blood (37). Horvath (46) proposed that in old people the sampling of capillary blood was more accurate and easier. In work done by Hamman and Hirschman (39) the authors found that it was more disagreeable for patients to be stuck in the ear or finger tip than by the venipuncture skillfully done. Other authors use the venipuncture method entirely.

The question of the frequency of withdrawing blood samples has also aroused some discussion. Ross (90) feels that since the deviation of the curve usually begins in five minutes and reaches a peak in twenty to thirty minutes, a blood sample should be taken every twenty minutes during the first hour and every half-hour afterwards. Horvath (46), using the capillary blood sampling method, takes samples every fifteen minutes during the first hour and at half-hour intervals thereafter for three hours. Hale-White and Payne (37) suggested that samples be taken every fifteen minutes for the first one and one-half hours to closely check the rise of the curve and the time the peak was obtained and that sampling be for at least two and one-half hours.

Jacobsen (50) found that the normal blood sugar in the healthy adult rises sharply and to a maximum level of 0.16 percent or more in thirty minutes and falls to normal gradually in one to three hours. Marshall believes that the level should not exceed 0.15 percent and should be reached in thirty minutes. He also believes that the fasting level should be reached in one to two hours (73).

In old age the body operates on a pattern of economy without waste. The characteristic physiological reaction in later life is a condition of minimal rather than maximal activity (27). Intestinal absorption is slower even though complete (76). Possible disparities between absorption and utilization are shown by organ function tests. Normal wide range of adaptation inherent in the liver would suggest that it is quite able to function properly even in the old person.

Spence (99) was one of the first to show that dextrose tolerance diminishes with advanced years. Blood sugar curves of old men tested by Spence showed an average fasting blood sugar of one hundred and thirty-five milligrams percent. Another study (64) showed the fasting blood sugar to be in the normal range in sixty percent of the cases with hypoglycemic curves in ten percent and hyperglycemia in thirty percent of the cases. That the carbohydrate metabolism as measured by the blood sugar curves is definitely impaired in old age has been shown by Deren (21), Marshall (73), Spence (99), Hale-White and Payne (37), Amako (3), Hofstatter (44) and Porter and Langley (83). Punschel (84) in

Germany found the carbohydrate metabolism normal in old age. Bogdanovich (10) in Russia found a normal fasting blood sugar in the old age group but believed that the carbohydrate metabolism was slightly impaired. Freeman (27) considers this finding by most, that the carbohydrate metabolism is measurably impaired, to be significant. He believes the impaired metabolism of carbohydrates is due to the diminished ability to utilize the carbohydrate since he found that digestion and absorption proceed without major hindrance. He believes that the prolonged tolerance test may serve as an indication of the delayed physiological capacity of the body in later life. Study was done by Hofstatter (44) to determine as to whether this impairment of carbohydrate metabolism proceeds under the influence of ageing or decline alone or whether it is related to disease, but no definite conclusions were reached. Spence (99) believed that in old people the carbohydrate storage mechanism is impaired and becomes increasingly worse as age advances. Bogdanovich (10) believed the decreased tolerance in old age to be due to deficiency and decreased activity of the endocrine system.

A study of one hundred and fifty-four older patients showed delayed glucose tolerance curves in 27.8 percent and mild diabetic curves in 19.4 percent. Tests later on these same individuals showed progressive reduction in the glucose tolerance test (27) (44). Marshall (73) found the fasting level to be a little higher than normal; a high peak of 0.209 percent; and a peak reached in one hour instead of one-half hour. At the end of two hours, the blood sugar was still high (0.132 percent) and the storage defect was evident. At two and one-half hours the blood sugar as a rule had fallen a little below its fasting level. Hale-White and Payne (37) in their work on old people found that in subjects over seventy, it was not uncommon to find high peaks of 0.21 percent. Most of the cases showed some delay in returning to the fasting level. Normals were set at 0.22 percent at seventy years of age and 0.24 percent at eighty years of age. The level did not return to normal in three hours in any of the patients over sixty years of age.

Other authors (83) in tests on older patients believed that the blood sugar level tends to rise from normal (0.08 percent) in youth to a normal of

0.15 percent at seventy years of age. They also found that in most old people that there was a lengthening of the curve over a two and one-half to three hour period. They found in the decades seventy to eighty that the type of curve obtained differs greatly in that it does not rise so high and takes longer to return to normal.

Following the results shown by Hale-White and Payne in 1926, Marshall was able to classify the types of curves seen in men over sixty-five years of age. They were the normal adult curve, the storage defect curve, the lag curve, the flat curve and the typical diabetic curve. This review of the literature and personal investigation (73) added much to the present conception of carbohydrate metabolism as related to the glucose tolerance test.

He found the normal adult curve in fourteen percent of the cases. In this type of curve the blood sugar rises from a fasting level of 0.1 percent to a maximum of 0.17 percent in one-half to one hour from the time of glucose feeding. The blood sugar then falls and in one and one-half hours has reached or almost reached fasting levels. In

two hours the blood sugar is below the fasting levels as a rule.

The storage defect curve was found in thirty-nine percent of the cases. The sudden fall which occurs in the blood sugar of the young healthy adult one-half hour after it has risen is explained by the rapid conversion of glucose into glycogen by the liver where it is stored. If the liver storage mechanism is disturbed, there occurs lengthening in the glucose tolerance curve and this sign in the young may be an indication of potential diabetes mellitus. In the old patient this is quite normal. There is a storage defect present when the blood sugar has failed to return to normal fasting blood levels within two hours.

The "lag" curve was found in twenty-five percent of the cases. Occasionally in patients suffering from considerable glycosuria, the blood sugar level two hours after the dose of glucose is low due to low renal threshold. Maclean (70) described the typical curve. It begins from the fasting level of 0.10 percent, rises quickly in one-half hour to 0.214 percent; at the end of one hour it drops to 0.154 percent and in one and one-half hours reaches

0.098 percent. Urine from the beginning to the end of the test shows traces of sugar. At the end of the test, the urine contains 0.18 percent sugar. The mechanism for dealing with the glucose was quite active as shown by the fact that the blood sugar reached a point below the fasting level in one and one-half hours from the time of beginning. The normal mechanism which prevents the blood sugar from exceeding the threshold value is absent. This type of curve indicates no definite gross disturbance of the carbohydrate mechanism. It is quite often seen in elderly people.

The "flat" curve was seen in about seven percent of the cases. The glucose given orally is absorbed in the small intestine. The flat curve is due to decreased absorption of glucose. This may be due to diminished motility of the stomach delaying the passage of the glucose into the small intestine or may be seen in cases in which the mucosa of the small intestine may be so atrophic as to be incapable of absorbing glucose normally.

The typical diabetic curve was seen in fourteen percent of the cases. Here the peak doesn't exceed 0.24 percent and the blood sugar had not returned

to the fasting levels by the end of two and one-half hours. It is normal in a certain proportion of aged people.

In a comprehensive review of the literature until 1945, Hofstatter (44) classified findings of a great number of cases into eight classifications that seem more precise than the classification by Marshall in 1925. The new classification is more able to fit the types of curves seen in the old person than the previous grouping. Hofstatter classifies the different types or oral glucose tolerance curves as follows: (1) flat curve in which there is a normal fasting level and a rise of the blood sugar less than forty milligrams; (2) low hypoglycemic curve which shows moderate hyperglycemia but with a drop into the hypoglycemic area; (3) high hypoglycemic curve which is a mild diabetic curve with a normal fasting level but a hypoglycemic drop during the test period; (4) normal curve; (5) delayed return curve which has a normal fasting blood sugar but of amplitude not higher than one hundred milligram percent with the peak in the first hour. This curve however, does not return at the second or third hour; (6) delayed rise curve

in which the amplitude is not more than one hundred milligrams percent above the fasting level and there is a delayed appearance of the peak to the second or third hour; (7) mild diabetic curve in which the normal fasting blood sugar is present but a hyperglycemia of more than one hundred milligram percent from the fasting level is present after the test meal; (8) diabetic curve which shows hyperglycemia in all portions. A graphic illustration of the curves previously described by Hofstatter may be seen on Chart I, page 54.

Hofstatter also found that there was great variability in the tests being run and that the test varied in each individual from time to time. Horvath (46) in a more recent study of this problem feels that because of the great variability of results it is practically impossible to judge the degree of impairment of the carbohydrate metabolism in aged individuals. The failure to obtain duplicate curves in the older patients was believed by Horvath to be due to the mixed diet, but other authors found the same results even with standardized diets. The absorption of glucose from the gastrointestinal tract may be responsible for the lack of parallelism

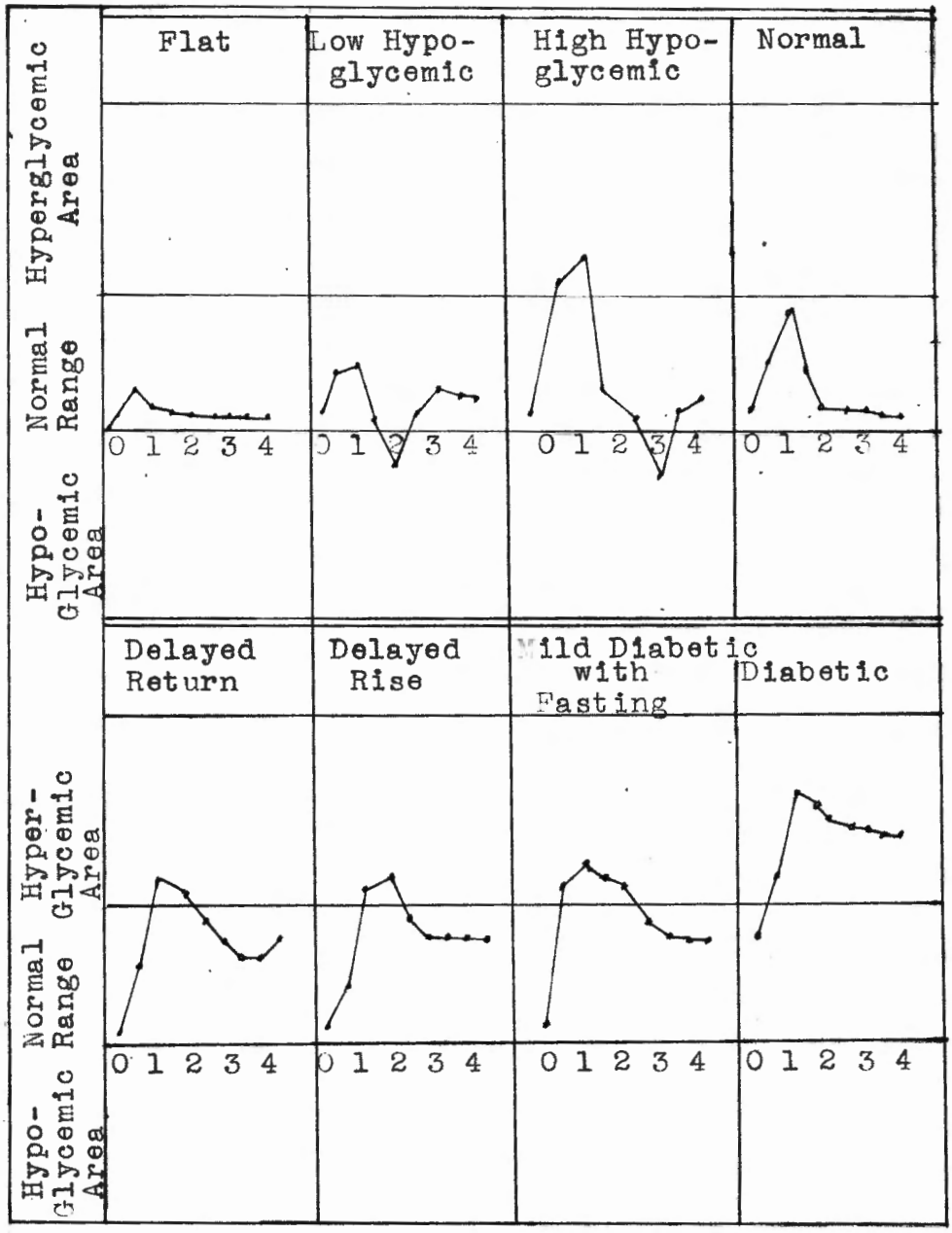
Flat
Low Hypo-glycemic
High Hypo-glycemic
Normal
Hyperglycemic Area
Normal Range
Hypo-Glycemic Area
0 1 2 3 4
Delayed Return
Delayed Rise
Mild Diabetic with Fasting
Diabetic
Hyper-Glycemic Area
Normal Range
Hypo-Glycemic Area

Chart I

in repeated curves. The pancreatic and hepatic reactions to the ingested glucose may also be at fault, but all of the potential factors point out the difficulty and complications in the analysis of the oral glucose tolerance curves in any age group.

Because of the vast variations met with the use of the above test, Exton and Rose developed a one hour, two dose dextrose tolerance test. This test is based on the paradoxical law of Allen (2) which distinguishes sharply between diabetics and non-diabetics. The limits of tolerance in non-diabetics are apparent, not real. Limits of tolerance in diabetics are real, not apparent. In normal individuals the more sugar given, the more is utilized; the reverse is true in diabetics. Hamman and Hirschmann (39) found that the normal humans react to repeated doses of glucose with either hypoglycemia or little or no change of glycemia, while diabetics react with definite hyperglycemia. The underlying physiology was explained by Mac Lean and de Wesselow (70) and Foster (26) who stated that the first dose of glucose stimulated the insulin-glycogen mechanism to such activity that the normal

organism was then able to deal with any amount of sugar without becoming hyperglycemic. Diabetics react with definite hyperglycemia because the insulin-glycogen mechanism fails (24) (14).

It was shown by Sweeney (101) that in the old type of glucose tolerance test the antecedent diet was an important factor. The new test implies that the antecedent diets or food habits do not influence the results. Nielsen (79) concluded that there should be no change in the diet preceding the test so that the test would be run under usual conditions not depriving the subjects of accustomed food. Exton and Rose ran the tests with and without special diets or fasts and got the same results.

Kelly (55) found excellent results with the Exton-Rose test. Young (110) found this test in error and several other authors found the tests equally accurate (58). Langner and Deweis came to the conclusion that the Exton-Rose test was usually more sensitive than the previous method and thought that it was more specific for diabetes. They accepted the criterion of Mathews (74) which is more sensitive but less specific than that of Gould (33). Mathew's criterion stated than an

individual with a one hour blood sugar value in excess of one hundred and sixty milligrams per-cent (Folin-Wu) should be suspected of having diabetis. In Gould's criterion a rise of thirty milligrams percent is allowed in the second half hour.

As the time passed, more and more work was done with the Exton-Rose test. In 1946, Langner reviewed the pertinent literature (60) and pointed out certain discrepancies which indicated that the Exton-Rose test was less reliable than the conventional one-dose test. Other authors, (98) (107), however, still believed that the test was a worthwhile procedure.

In arriving at the conclusion that a second fifty gram dose of glucose would have an appreciable effect on the blood sugar curve in the half hour time, Langner believed that Exton and Rose failed to consider certain physiological facts; namely that (1) the rate of absorption of glucose from the intestinal tract; (2) the rate of utilization; and (3) the natural shape of the glucose tolerance curve after giving one hundred grams of glucose would be the same whether in one dose or two doses.

Cori (19) in an extensive review of the literature found that the maximum rate of absorption from the intestinal tract in man is 0.85 grams per kilogram, or about sixty grams per hour, for the average size man. The Exton-Rose test supplies twice as much as can be absorbed in one hour. Groen (35) believes the absorption of fifty grams of glucose would take four hours, but Langner thinks this is too conservative. Groen also believes that, if glucose were introduced directly into the whole intestine, a greater absorption would occur. However, when glucose is given by mouth, the pylorus takes care that absorption does not take place at a rate which exceeds the capacity of the storage mechanism. Ravdin (86) found that when glucose solutions of varying concentrations from 3.5 to fifty percent are placed in the stomach, the concentrations obtained from the jejunum and ileum at the end of one hour are markedly constant and do not exceed 5.3 percent. Thus the stomach protects the intestines from receiving too much glucose in too great concentrations. From this work, the conclusion may be made that the mechanism for the utilization of sugar by the tissues is not greatly accelerated until blood sugar reaches

a certain concentration. The activity of the mechanism increases as the blood sugar rises higher, until at the peak of the curve the utilization rate overtakes, and then surpasses the rate of absorption. This occurs in spite of the fact that the absorption may still remain at its maximum. The accelerated utilization, once speeded up does not stop until the blood sugar has become subnormal. If there is more glucose in the intestine the absorption continues for a longer period of time but the rate of absorption is not increased (19).

In view of the above information, there would seem to be no rationale in the giving of the second dose at the height of the blood sugar curve, since in a normal individual the curve would fall whether a second dose were given or not. In a diabetic the curve would continue to rise whether a dose were given the second time or not, so that any difference in effect from the one dose test would not be manifest in one hour.

Several authors (15) (59) (101) (102) believe that the one and two dose tests have no physiologic difference, and that there is no advantage of doing the Exton-Rose test except that it takes less time

to complete the test. One hundred grams of glucose is dissolved in six hundred and fifty cubic centimeters of water, flavored with lemon and divided into two equal parts containing fifty grams of fifteen percent solution. Urine and blood are collected before the test, at thirty minutes and at one hour. Interpretation of the first part of the curve (the original and thirty minute specimens) is the same as the old method. The interpretation of the second part (from the thirty to the sixty minute specimens) is different. The curve rises in about thirty minutes to one hundred fifty to one hundred sixty milligrams percent. The one dose test is usually higher but due to better absorption of the two dose test, the latter results may be higher. The second part of the curve of the Exton-Rose test shows a greater fall of the blood sugar than occurred in only the single dose test. In diabetics there is a steep climb in the curve after the second dose.

Because of the many uncontrollable factors present in either of the oral glucose tolerance tests, the intravenous test was developed. The advantages of the intravenous glucose tolerance

tests, the intravenous test was developed. The advantages of the intravenous glucose tolerance test are (a) there is a controlled time of injection of the glucose; (b) the time the introduction ceases is known; (c) there are less variations than with the oral test; (d) an accurate dosage may be injected as there is no loss due to failure of absorption from the intestine; (e) it obviates any anorrexia or nausea; (f) there is less variation in the curve from time to time and (g) the curve is much smoother. The disadvantages of the intravenous type test are that (a) it takes more time and is more trouble for the investigator; (b) there are occasional reactions; (c) injected glucose may have a less stimulating effect on the carbohydrate metabolism; and (d) theoretically it is less physiologic. In the oral test the blood goes to the liver first before going out into the system; whereas in the intravenous test this is not true (62) (54) (12) (67) (16).

In the intravenous method, what is the immediate fate of the injected dextrose? Is it excreted, stored or metabolized? The complete answer is difficult because there is the possibility of removal in two stages, the immediate and the late,

as suggested by the blood findings. Tunbridge and Allibone (104) investigated this subject and found the highest blood sugar value was recorded forty-five seconds after the end of the injection. The duration of the injections in their cases were two minutes thirty seconds. Assuming the blood volume of the normal person to be five liters, the blood sugar immediately after injection of twenty-five grams of glucose should be approximately six hundred milligrams. In other words, within approximately two minutes of the mean injection time ten grams or forty percent of the injected dextrose had been removed from the blood stream. It is difficult to believe that this has all been metabolized. The authors found that the amount of glucose lost by the kidneys cannot account for the rapid disappearance from the blood volume. Other authors (8).(75) have found that when glucose is injected some of it can be accounted for by the increase in the liver glycogen, some is converted to muscle glycogen, some is oxidized (increased insulin activity is demonstrable in the blood of the pancreatic vein soon after injection of the intravenous glucose), some passes into the soft tissues

temporarily by process of diffusion, and some is changed to non-reducing substance in the blood.

The first study of injection of sugar into veins is that done by F. J. von Becker (90) in 1854. By this means glycosuria was observed. No clinical use was made of this until 1913, when investigators in Germany first published results of curves obtained by giving injections of seven percent glucose solution. In 1915 Woodyatt, Sansum and Wilder (109) felt the necessity of eliminating the unknown absorptive factors by using the intravenous route. In the main, two methods have been used. The first is the continuous administration of a weak solution of dextrose; the second is the rapid injection of a more concentrated solution. Best (7) believed the continuous method to be the best but advocated administration of fixed doses at regular intervals as being most likely to give the most useful information. Blumenthal first used the continuous intravenous method. The method of single injection has been widely employed by many authors.

One of the first procedures suggested was that by Tunbridge and Allibone (104) in which ninety-

two cubic centimeters of a thirty percent solution of dextrose dissolved in distilled water was injected into the median basilic vein in three minutes. The injections were made in the morning on patients who had fasted all night. Blood samples of 0.1 cubic centimeters were taken from the lobe of the ear at intervals of one and one-half to seven and one-half minutes for at least sixty minutes after the end of the injection. The ear was selected as it was easy to manipulate. This procedure was used because by the micro-interval technique the test would have necessitated too many venipunctures to be practicable in the private patient (75).

In another method, Hofstatter used fifty cubic centimeters of thirty percent glucose and injected this within exactly two minutes. Venous blood samples were taken at fasting time, four, seven, fifteen, thirty, sixty, and one hundred minutes after completion of the injection (44).

Lennox (61) used twenty-five grams of glucose intravenously and believed that in this case he was receiving best benefits in giving maximum stimulation to the carbohydrate mechanism.

In further study, Tunbridge and Allibone (104)

found maximal values of the curve at the immediate end of the injection. The curve was seen to fall rapidly during the first twenty minutes, reaching the fasting level in approximately forty-five minutes. This was then followed by a definite hypoglycemic phase before returning to normal.

Lennox (61) reported that the repetition of the intravenous administration over a period of months led to an increased rapidity in the disappearance of the dextrose. He also found that no variations in the maximum blood sugar value, the form of the curve, or in the time taken to return to the fasting level value could be attributed to variations in weight. He stated that the amount of dextrose injected, the duration of the injection and the effect of age were all important factors. Most authors have obtained similar results with the intravenous glucose tolerance test as with the oral methods in the old patients. Both indicated a decreased tolerance.

The chief complications reported in the intravenous glucose tolerance test series of Tunbridge and Allibone (104) were pyrexia, rigors, general malaise, headaches and shivering. None of the

reactions were severe enough to require medical treatment.

Of great importance in the glucose tolerance test, as with all blood chemistry determinations, is proper preservation of the blood specimens from the time that they are drawn until the time that they are examined in the laboratory. Many methods of preventing glycolysis in blood samples have been used, but the method developed by Lewis and Mills (65) gives best results at present. These authors use potassium fluoride and monochlorbenzene and have found there is practically no variation in blood chemical constituents in oxalated specimens when kept at six degrees centigrade even at the end of ninety-six hours. Rose and Schattner (89) prefer the use of sodium fluoride and chlorobenzene. These authors believe that with this preservative, no appreciable fall of the blood chemical constituents will occur during the first day but that the glycolysis will increase markedly in the succeeding days.

Summary

1. An introduction into the subject of geriatric problems has been made, showing the need for such a study.

2. Pathological changes in the senile liver were described.

3. A discussion of carbohydrate digestion and absorption was made.

4. The mechanisms of regulation of the blood glucose level were presented, showing the relationship of the endocrine glands to carbohydrate metabolism.

5. The methods of formation of the blood sugar were described.

6. The oral one dose, oral two dose (Exton-Rose) and intravenous glucose tolerance tests were reviewed in detail with discussions of their mechanisms, procedures and results with special application to the geriatric patient.

Conclusions

1. The glucose tolerance test is the simplest procedure available for studying the integrity of the entire mechanism of progressive carbohydrate metabolism from ingestion through absorption, storage, availability and oxidation.

2. The glucose tolerance test is a reliable measure of determining the efficiency of carbohydrate metabolism in the old age patient.

3. Carbohydrate metabolism is closely regulated by the endocrine system.

4. Carbohydrate metabolism is impaired in old age, as shown by a lowered tolerance to glucose and a higher, more prolonged type of glucose tolerance curve.

5. Impairment of carbohydrate metabolism in old age is due to diminished ability to utilize carbohydrates, decreased activity of the endocrine system, and decreased liver function which is a characteristic physiological reaction in later life in which minimal rather than maximal activity is maintained.

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