Spontaneous hypoglycemia : a discussion of etiology, symptomatology, and therapy

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SPONTANEOUS HYPOGLYCEMIA

A discussion of Etiology, Symptomatology, and Therapy.

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A Senior Thesis presented to the College of Medicine, University of Nebraska, Omaha, 1937.
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INTRODUCTION

The term hypoglycemia, as defined by Dorland is "a deficiency of sugar in the blood". He defines spontaneous as "voluntary, instinctive, or occurring without external influence". By spontaneous hypoglycemia, then, we mean a deficiency or lowering of the blood sugar below normal levels occurring without any external influence. The term "paroxysmal" hypoglycemia was suggested by Wilder (168) in 1936, which he believes better describes the syndrome.

This entity must be differentiated from the well known insulin reaction first recognized and described by Banting and coworkers (7, 8), and Fletcher and coworkers (48), which occur because of an overdose of insulin injected parenterally. This, by virtue of its external influence, is not hypoglycemia developing spontaneously, and consequently will not be discussed in this paper. It was these reactions, however, that keen observers noted in patients who never had insulin injections, that has led to the recognition of this relatively new disease entity.

Since spontaneous hypoglycemia was first recognized in 1923 by Seale Harris (64), there has been a wealth of literature written on the subject. Many disease conditions of the endocrine glands have been found where there is a disturbance in carbohydrate metabolism resulting in symptoms of hypoglycemia. In many other diseases not particularly involving the endocrine glands, and physiological states, low blood sugars with accompanying symptoms have been observed. In many of these the symptoms of hypoglycemia have been the incapacitating factors rather than the disease condition itself.
This syndrome is not generally recognized as often as it should be, when the frequency of its occurrence is considered. Many clinicians who conducted investigations of their records, did routine blood sugar studies or were particularly watchful for the symptoms, have found that it is nearly as frequent as the opposite condition diabetes mellitus (hyperglycemia).

The symptoms and manifestations of this entity are essentially identical to the well-known insulin reactions, which are quite universally familiar to those in the practice of medicine.

Explanation of these symptoms and etiological factors have come largely from the investigations of carbohydrate metabolism, physiology of the endocrine glands, neurology, and advances in blood chemistry. Due credit, then, must be given to those investigators who have contributed to our present knowledge; for without their work no explanation of the condition nor treatment for it would be possible other than on an empirical basis.

The treatment of the various phases of this entity has advanced as well as the recognition of the etiology. At present the situation may be coped with satisfactorily in most cases.

Therefore, because of the increasing amount of literature on the subject, because of the frequency of its occurrence, because of the lack of general recognition, and because of the effective methods of treatment, an investigation of the literature has been undertaken in order to sum up as far as possible the present knowledge of this syndrome.
A somewhat brief historical account is given, as well as a brief discussion of the physiology concerned to further promote understanding of the subject. The present discussion is limited to the etiology, symptomatology, and treatment of the entity. The pathology, details of technique, and pathological physiology have been largely omitted. No original contributions are made.
During the fifteen years that have elapsed since Banting and Best isolated insulin in 1922, hypoglycemia has become a familiar clinical syndrome. The order of its discovery was unusual, if not unique, in the history of medicine, for it was first recognized in the exhibition of a new therapy and was afterwards found to occur as a result of natural causes.

In the seventeenth century the sweetish taste of diabetic urine was discovered by Thomas Willie. The presence of a sugar-like substance in the blood was first shown by Mathew Dobson in 1775 in a case of diabetes. He proved that the sweetness of the urine and blood serum in diabetes was due to sugar in 1776.

In 1845 Claude Bernard showed that this sugar-like substance discovered by Dobson was a constituent of normal blood and also demonstrated that the amount of this sugar was increased by his well known "sugar puncture" of the fourth ventricle.

Claude Bernard was the first to suggest the regulatory function of the liver in the sugar supply to the blood, it being warehoused in that organ and given to the muscles as demanded by their work. When he produced glycosuria by puncture of the floor of the fourth ventricle, he demonstrated the control of the nervous system over the output of sugar from the liver.

The fact that blood sugar may be reduced or absent has been known since 1849. Claude Bernard demonstrated it in experimental animals thus pointing the way to almost every subsequent discovery about carbo-
hydrate metabolism. Experimental means had been found for producing the condition of low or absent blood sugar prior to the isolation of insulin. Claude Bernard 1849 and Kaufman 1895 (162), prevented the glycogen stores of the liver from reaching general circulation by the section of the nerve supply of the liver. The same was done by Seegan in 1890 (152) by ligature of the aorta and vena cava above the diaphragm. Mann and Magath in 1921 (105), showed that when the liver was removed from the dog, the sugar in the blood disappeared and the dog died in hypoglycemic shock.

Minkowski in 1893 (159), founded the basis for belief that there was an internal secretion of the pancreas having a controlling influence on carbohydrate metabolism. This was done by expirpation of the pancreas.

Minkowski in 1892, and von Mehring in 1899 (162), produced hypoglycemia by the administration of phloridzin, which lowers the renal threshold and allows overflow glycosuria. The blood sugar is reduced and the liver depleted of glycogen. This condition is similar to renal diabetes in human beings.

In 1902, Merter and Richards (159), discovered that injection of adrenalin chloride into dogs produced a transient glycosuria, also that direct application of adrenalin to the pancreatic surface did the same. They first said this was pancreatic in origin, later finding that it was not due to the pancreas but to the adrenalin itself.

Frank and Isaac in 1911 (102) found that phosphorus poisoning low-
ered the blood sugar in rabbits by damaging the liver; combining phosphorus and phloridzin produced severe hypoglycemia. In 1911 Underhill (153) found that hydrazine poisoning had a similar effect as the phosphorus and phloridzin. Underhill states that with the exception of phloridzin glycosuria little has been known concerning the conditions necessary to diminish the content of the blood sugar. In 1916 (157) he also lowered the blood sugar in rabbits by altering the acid base equilibrium through the administration of calcium salts, trisodium phosphate or sodium carbonate. H. Bierry and L. Malloizeel in 1908 (152), found that removal of the suprarenal glands reduced the blood sugar in dogs from .13 percent to .088 percent within three and a quarter hours. O. Forges in 1910 (152) obtained considerably lower figures e.g. .033 and .032 percent in nine and thirteen hours respectively.

Hypoglycemia in man prior to the use of insulin in 1922 has been recognized in three distinct conditions.

In 1910, O. Forges (152), who was the first to observe hypoglycemia in man, reported three cases of Addison's disease in which blood sugar levels were .067, .052, and .033 percent respectively.

In 1912, H. Cushing (39) published a case (no. 23) of pituitary tumor, in which the fasting blood sugar was .039 percent. The adrenals were thought to be involved also due to the pigmentation and asthenia of the patient. Against this was the systolic blood pressure of 140 m.m. of mercury. This case of Cushing was one of pituitary insuf-
iciency, and is the first one showing a positive hypoglycemia. He states that the only other malady causing this that he knows of is Addison's disease. Cushing says that Forges showed that hypoglycemia developed when the adrenals were removed in dogs.

Fischler (50) in 1913, first described hypoglycemia shock under the title of "glucoprivative intoxication" in dogs. He described the convulsions and weakness in rabbits while lowering the blood sugar by fasting and phloridzin and also use of an Eck fistula.

In 1916, R. H. McCrudden (110) found hypoglycemia associated with cases of muscular dystrophy of the progressive type.

Janney, Goodhart, and Isaacson (80) in 1918, in their investigation of muscular dystrophy deemed it justifiable to regard muscular dystrophy a result of dysfunction of the endocrine glands, and there stated that the abolition of an endocrine gland would lead to hypoglycemia.

E. P. Joslin in 1921 (88), published three cases in diabetic patients on the low carbohydrate diet where exhaustion of glycogen reserves was associated with hypoglycemia. In one case no. 1831 the blood sugar fell to 40 mg. percent. Joslin also states that the discovery of hypoglycemia during course of treatment of diabetes by undernutrition is a danger signal of the first importance (88).

In 1921 Raphael, Theophile, and Parsons (135) found that ten out of eleven patients of the dementia praecox group had fasting blood sugar below normal. Those in the hypomanic phase of the manic-depress-
ives also showed hypoglycemia.

From this short discussion we see that the biological fact of hypoglycemia was known to laboratory workers, and had been reported as a rare occurrence in clinical medicine. Hypoglycemia was not associated with a definite symptom complex until after the discovery of insulin and the results of its over-doses were observed.

In 1922, F. G. Banting, and C. H. Best, (6)(7) found that their extract of the pancreas invariably produced in rabbits hunger, thirst, hyperexcitability and fear, and finally convulsions at .045 percent of blood sugar. They found that purified alcoholic extracts of the islands produced a lowering of the blood sugar in normal rabbits. They suggested the name for this substance as insulin. (7)

As soon as insulin was made available for the treatment of the diabetic patient similar symptoms in man were observed. Banting, Campbell, and Fletcher in 1923 (8) were the first to make these observations. They found that in treating a diabetic patient hypoglycemic reactions may occur. They found in that when a single injection is given to a patient there is a rapid fall of blood sugar which reaches a low point in two to eight hours, and tends to return to the original level in twelve to twenty-four hours. They state that while the extent of this fall is dependent in a measure on the amount of insulin and upper initial blood sugar level, it cannot be predicted with any great degree of accuracy in an individual patient. Since they were the first to note with accuracy the symptoms of overdosage with insulin, I believe
it fitting to record here their observations. They found that when the blood sugar reached 70 mg. percent under the influence of insulin, the patient became aware of it by symptoms of hunger, weakness, fatigue, nervousness, crying spells, tremulousness, and vasomotor phenomena of pallor or flushing and sweating. When 50 mg. is reached the patient has acute distress, mental confusion and disorientation. When 32 mg. percent, coma results with loss of reflexes. These symptoms were found to be relieved by food or orange juice and epinephrine intramuscularly.

The entity of hyperinsulinism itself has an interesting history. With recognition of insulin reaction by Banting, Campbell and Fletcher, the eyes of the profession were opened and soon the same symptom complex was found in non diabetic patients and without the administration of insulin. Seale Harris (64), in October 1923 reported two such cases and in 1924 five cases were considered under the origin of hyperinsulinism and dysinsulinism. It was by Harris that these two terms were introduced for the condition of hypoglycemia arising from hypersecretion of the islands of Langerhans. At this time Harris referred to the condition of hyperinsulinism as being perhaps a disease entity with the symptoms of hypoglycemia. The pathological basis was not verified by Harris.

The next important landmark in the history was set up by Wilder, Allen, Power, and Robertson (166), in 1927. They described a case with the symptoms of hypoglycemia, the blood sugar going as low as 20 mg. percent. Operation was advised and a carcinoma of the pancreas was
found with secondary tumors in the liver. From the tumor tissue both from the pancreas and liver, insulin was extracted. This case was the first to prove that carcinoma may arise from the islands of Langerhans, and also proved that hypersecretion of insulin can cause hypoglycemia.

In 1928 Finney and Finney (47) reported a case of hypoglycemia treated with improvement by surgical removal of two thirds of the pancreas. The pancreas was morphologically normal. They considered the case of hyperinsulinism on a functional basis.

Thalhimer and Murphy in 1928 (151), reported a case of carcinoma of the islands with marked hypoglycemia. No extracts were made to confirm it pathologically.

McClenahan and Norris in January 1929 (109) reported a case of periodic hypoglycemia due to a benign adenoma of the islands of Langerhans. The pathologic diagnosis was made at autopsy.

In August 1929, Howland, Campbell, Maltby, and Robinson (77) reported a case of hypoglycemia in which at operation a slow growing carcinoma of the islands of Langerhans was found at operation. Insulin was extracted from the removed tumor. The patient was cured by the operation, as no metastases were found. This is the first instance of cure by surgical removal of carcinoma of the islet tissue of the pancreas.

Thus by 1929 we find that spontaneous hypoglycemia was a sufficiently definite disorder to justify surgical intervention.

Some other earlier workers in their field should be recognized here. In 1924 Levine, Gordon, and Derick (95), noted that the appear-
ance of exhaustion which some athletes manifest following a run or crew race was strikingly similar to insulin shock. It was found that those showing these symptoms did have low blood sugars and manifest symptoms of hypoglycemia. Talbot and Shaw and Moriarty in 1924 (148) gave the first report of hypoglycemia in children. They reported it occurring in conditions of acidosis resulting from starvation and deficient blood sugar. Clark in 1925 (32), found that stimulation of the vagus nerve produced a decrease in the blood sugar of dogs. Shih-Hao in Peking China in 1925 (143), described hypoglycemia in children that were dehydrated by diarrhea, purging, and starvation. Gray and Feemster in 1926 (61) gave the account of a child born of a diabetic mother. They showed by autopsy findings, that the islands of the child were increased 24 fold. This is the first time that such a sequence has been observed in this completeness.

Nielsen in 1926 (121), found the occurrence of hypoglycemia in patients with an imbalance of the vegetative nervous system namely vagatonia.

It was Gammidge in 1927 (24), who by his breeding experiments with mice, showed apparently that a low blood sugar was a recessive character and transmitted according to Mendel's theory of heredity. He states that the cause appears to be a relative hypersecretion of the islands of Langerhans. The hereditary nature hasn't been proved in humans, but he points to the frequent occurrence in several members of the same family--especially when it occurs in childhood. This was the
first work done of this nature.

Titus and Dodds in 1928 (154) found the occurrence of sudden drops in the blood sugar at the time of eclamptic convulsions in pregnancy. Longcope (97) associated hypoglycemia with scleroderma in 1929. Josephs in 1926 (87), reported hypoglycemia in children with recurrent or cyclic vomiting. Cammidge in 1931 (26), stated that low blood sugar was a common feature of allergic disease in his presentation of cases of bronchial asthma. In 1933 Barrow (9) reported the first case of hypoglycemia treated with temporary cure by the use of the Roentgen ray.
In order to understand the various mechanisms by which pathological conditions cause a disturbance in the controlling factors of blood sugar, a brief review of the physiology of these factors should first be given. C. H. Best in a recent article (13) gives the physiology of the pancreas in a way which in my reviews of this subject have not found the equal. I shall quote this article. Details that are omitted may be obtained by referring to this article. Additional physiology where needed is inserted in the proper section.

"The time honored and productive physiologic methods of studying the function of an organ are, (1). To remove it completely or in part to observe the abnormal effects attributable to the absence, and (2). to make extracts of the tissues in various ways and to study the mechanism of action of the fractions that are found to possess specific physiologic potency. The pancreas has lent itself well to this procedure especially in the case of the internal secretion.

**Removal of the pancreas.**

"When the pancreas is removed from a dog, a characteristic syndrome results. If the diet is adequate and insulin is supplied the animal may live indefinitely. When insulin is discontinued the diabetic state quickly supervenes. The blood sugar rises quickly and increases from a normal level of from 0.08 to 0.11 percent, to 0.20 to 0.40 percent or higher in 24 hours. The urine gives a positive test for glucose when the blood sugar rises above approximately 0.16 percent. This point, the so-called renal threshold, is the level of blood sugar above which
large amounts of sugar are secreted into the urine. This threshold may rise if high blood sugar is permitted to exist. In the fasting diabetic the blood sugar and excretion are maintained at high levels. The sugar is apparently formed from body protein largely in the liver, since the blood sugar of the diabetic subject falls rapidly after hepatectomy. The loss of protein contributes to rapid decrease in weight of depancreatized animals.

The disturbed fat metabolism of fat in the depancreatized animal is indicated by the accumulation of the ketone bodies in the blood and by the excretion of excessive amounts in the urine. Formation of acetoacetic acid is toxic. It stimulates the respiratory center and depresses the higher centers of the brain causing "air hunger", and the dimmed perception and loss of consciousness of diabetic coma. Aceto-acetic acid is probably not the only product that causes this.

There is a rise in the cholesterol content of the blood, also a rise in neutral fat probably due to augmented rate of mobilization of fat depot. When the rate of breakdown of the fatty acids is excessive, as in pancreatic diabetes these ketone bodies accumulate in the blood.

In the diabetic animal there is both an increased production of sugar as well as underutilization of sugar.

Glycogen content of liver and muscle especially the former is marked. Phosphate excretion is increased in the depancreatized animal. The diabetic animal is susceptible to infections, the reason for this hasn't been proved to be the increased sugar content of tissues.
The specific antibodies aren't altered, but other defense mechanisms may be made less effective by the abnormal metabolic condition. Without insulin the animal lives about two weeks. With the anterior pituitary removed too, the animal may live for a year. Severe diabetes is produced under these conditions by the administration of the diabetogenic substance of the anterior pituitary, but the maximum duration of this form of diabetes is not yet established. It is alleviated by insulin.

**Effects of the Anti-diabetic Hormone—Insulin.**

"It is well established that insulin restores to the depancreatized animal its ability to metabolize sugars and fats in a normal manner. The excessive breakdown of protein is prevented. The ketosis rapidly disappears. Glycogen accumulates in large amounts in the liver. Muscle glycogen may be increased; the respiratory quotient rises when sugar is made available or in fact when insulin alone is administered. Animals recover their ability to deal with infective agents. In brief, a well treated depancreatized animal is difficult to distinguish from a normal one. There is always the difficulty, of course, that in the animal without a pancreas relatively large amounts of insulin are made available two or three times a day, while in the intact animal small or large amounts are presumably liberated from the pancreas as the need arises or conceivably at an approximately constant rate."

**Source of insulin.**

"While it is reasonable to suppose that small amounts of insulin are present in tissues other than the pancreas, methods are not yet
available for their detection. Blood provides an exception to this generalization, but the active substance is detected by the intravenous administration of the whole blood and not by extraction of the insulin from the tissues. At least six groups of investigators, including the early workers on insulin in Toronto, were led for a time by errors in testing and by artefacts to believe in the wide distribution of appreciable amounts of insulin. In the mammalian organism the pancreas appears to be the only organ that manufactures or stores insulin.

The alpha and beta cells of the islands of Langerhans have been extensively studied and a third type, the gamma cell, has been detected. The beta cells, which occupy the periphery of the islets and whose granules are soluble in alcohol, are thought to be the source of insulin.

The main points of evidence which indicate that insulin is produced in the islet cells are as follows: 1. The active substance is found in degenerated pancreas in which the loss of acinous tissue has proceeded much more rapidly than that of the islet cells. (6); 2. There are relatively large amounts of insulin in the principal islet of teleostean fishes, in which few enzyme-producing cells are found. 3. Histologically, the islet cells are glandular structures the obvious outlet for the secretion of which is through the blood stream. 4. When large amounts of carbohydrates are given to partially depancreatized dogs, characteristic lesions are found (hydropic degeneration) in the beta cells, which disappear when the carbohydrate is eliminated from the diet or is balanced by insulin. 5. In the clinical condition
known as hyperinsulinism, the pancreas liberates abnormally large amounts of insulin. In many of these cases there are definite tumors of the islet cells. After the operative removal of these masses of islet cells the blood sugar is maintained at higher levels." (13)

Liberation of Insulin.

"The arrangement of the capillary loops about the islet cells and the reported scarcity of lymph channels provide morphologic evidence in favor of the capillary blood stream as the pathway by which insulin reaches the systemic circulation. It is important to remember that insulin passes first to the liver.

While there are many pieces of experimental evidence which support the conclusion that the level of blood sugar is an important factor in the regulation of insulin liberation, the possibility that a decrease in the rate of discharge of sugar from the liver may also be produced when the blood sugar is raised is frequently overlooked. Increased deposition in or utilization by muscle is probably not an important factor in these very short experiments. When insulin liberation is maintained at a constant level in the depancreatized animal, the curve of blood sugar following an injection of dextrose may be very similar to that obtained in an intact animal, the curve of blood sugar following an injection of dextrose may be very similar to that obtained in an intact animal. Removal of the liver produces the diabetic type of curve. However, the injection of small amounts of dextrose into the artery supplying the pancreas grafted into the neck of a depancreatized dog or
into the pancreatic artery in a decerebrate cat causes a prompt lowering of blood sugar. In the latter case the effect was not obtained when the splenic or portal vein was used. If these results on decerebrate cats can be accepted, they provide evidence for the chemical control of insulin liberation through action of dextrose on structures within the pancreas, but the effect of a raised blood sugar on the rate of discharge of dextrose from the liver must also be considered. The results of experiments with denervated pancreatic grafts suggest that the pancreatic effect is exerted directly on the islet cells. These manifestations indicate that the nerve control is not essential. The nerve impulses that affect the islet cells are apparently conducted by the vagus. Vagus fibers have been traced to the islet cells, and nonmedulated branches are said to pierce them. The results of stimulating the vagus appeared to be clear cut and the pathway was traced by one group of investigators to the hypothalamic region, but other workers have as yet been unable to confirm these observations. The effect of vagus impulses on the rate of sugar production by the liver requires further investigation, but the possibility that this mechanism is the one effective in lowering blood sugar must be considered."

**The Mechanism of Action.**

"In the diabetic patient there is evidence that insulin enables more sugar to be burned, since the oxygen consumption is increased and the respiratory quotient rises. Some of the dextrose that disappears may be accounted for by the rise in liver glycogen, and there may be an
increase in muscle glycogen. Increase of glycogen and rate of oxidation apparently account for all the sugar that disappears. The decreased nitrogen excretion indicates inhibition of glyconeogenesis.

In the normal animal the slight increase in oxidation and the deposition of glycogen in muscle apparently account for practically all the sugar that disappears. In adult animals of all the species that have been studied, liver glycogen does not increase. (Cori, C. E. cited). The increase in liver glycogen in young rabbits is a secondary effect probably due to liberation of epinephrine. It has been argued that the deposition of muscle glycogen represents only an effect of abnormally large amounts of insulin, but small doses do not cause the disappearance of sufficient dextrose, in addition to that which is oxidized, to provide building material for the minimum glycogen increase, which can be accurately determined. Convincing direct evidence that large doses of insulin inhibit glyconeogenesis in the normal animal is not available, but this possibility is strongly supported by the results of several series of experiments."

Interference with the Action of Insulin.

Other hormones.— "There are five internal secretions the action of which may be considered antagonistic to that of insulin. There is no evidence of any chemical interaction of these hormones with the antidiabetic substance. Epinephrine causes a prompt mobilization of liver glycogen and probably somewhat later the conversion of muscle glycogen to lactic acid, which is in turn converted to dextrose or glycogen or
both in the liver. The suggested action of epinephrine in inhibiting oxidation of dextrose is not well supported by experimental evidence.

Removal of the adrenal cortex leads in some species to hypoglycemia, which is alleviated by injection of extracts secured from cortical tissue. The mechanism of such extracts is not established.

Thyroxine, by making liver glycogen more easily mobilized and also probably by accelerating glyconeogenesis, tends to produce hyperglycemia. On the other hand, the increased oxidation of dextrose in the tissues of a thyroxinized animal exerts the opposite effect on blood sugar. In the first stages of hyperthyroidism there is hyperglycemia and a decreased effect of insulin. In the later stages there may be severe hypoglycemia without insulin and a great susceptibility to the anti-diabetic substance. (Gites J. H. Burn 1925)

While posterior pituitary extract raises blood sugar and interferes with certain of the actions of insulin, it is not established whether the oxytocic or the pressor or both exert the effect. Furthermore, the evidence as to whether or not posterior pituitary extract acts through the adrenals is still controversial.

In certain species, at least, the diabetogenic substance of the anterior pituitary appears to be a very powerful antagonist of insulin. Hypophysectomized dogs, even after removal of the pancreas, may exhibit profound hypoglycemia. They are very susceptible to insulin. The information at present available indicates that the liver is essential to the action of the diabetogenic substance, which acts by stimulating
glyconeogenesis, in a large part at least." (Houssay and Baisotti 1931 are cited.)

Liver.

The liver has more than ten functions, but one of the most important is that concerned with sugar metabolism. It not only acts as a storehouse of glycogen, but acts in converting sugar from other sources such as protein. (13) The greatest works on the relationship of the liver to carbohydrate metabolism have been done by Mann and Magath (105,106,107). Through their experiments on extirpation of the liver in dogs, they proved that the liver was responsible for dextrose being in the blood. They showed that when the liver was removed from a dog the blood sugar disappeared and the animal died in hypoglycemic shock. That when the sugar was replaced intravenously the dog lived till it died of hepatic insufficiency. They also showed that hypoglycemia followed the removal of pancreatectomized animals, and that hypoglycemic symptoms appeared sooner and at a higher level if the blood sugar in those animals from which only the liver had been removed. The physiological connections of the liver with the adrenals and pancreatic islands have been mentioned. For detailed information I refer the reader to the works of Mann and Magath.

In review of this brief statement of physiology, it is quite obvious that the control of the blood sugar is indeed a complex mechanism. With so many influencing factors it takes very little imagination as to the possibilities of disturbance in this finely adjusted mechanism.
in man the normal level is different in different persons; in the
same person it varies at different times of day and in different states
of nutrition. (162) In children according to Spence (162), the blood
sugar is lower than in adults, suggesting how active the carbohydrate
storage mechanism is in very young people. Marshall (182) found that the
blood sugar in the elderly people was about 200 mg. percent, because
of the raised renal threshold and defective storage. According to
Joslin 1923 (89), "The blood sugar of normal individuals fasting, i.e.,
before breakfast, is most frequently .100 percent." Also,"The normal
percentage of sugar in the blood is .100 percent, but after a meal it
may rise to .16 percent without sugar appearing in the urine. The
adjustment of the mechanism by which insulin regulates the quantity of
sugar in the blood within these narrow limits is truly wonderful." (89)

Gray (60) found the average percentage for 431 observations com-
piled from many sources as .090 percent, the minimum being .04 percent
and the maximum .160 percent. J. Sigwald 1932 as quoted by Wauchope
(162), considers the fasting level to be in the very neighborhood of
.1 percent, and the lower limit of the normal,.095 percent. The max-
imum normal level after food is under .180 percent, the so-called renal
threshold, above which sugar appears in the urine. The levels at which
symptoms appear will be taken up under that section.
ETIOLOGY

PANCREATIC ORIGIN—HYPERINSULINISM AND DYSINSULINISM

Hyperinsulinism may be defined as "a disease of the pancreas resulting from spontaneous excess secretion of insulin by the islands of Langerhans, and characterized clinically by hypoglycemia with its concomitant symptoms, i.e., hunger, weakness, tremor, nervousness, sweating, trembling, and mental lapses, unconsciousness and convulsions may occur in the severe cases." (Harris)(66)

Dysinsulinism is defined "as a condition or disease, associated with the uncontrolled secretion of the islet cells of the pancreas resulting in hyperglycemia, alternating with or followed by hypoglycemia, and characterized clinically by symptoms of hypoinsulinism (diabetes mellitus), and at times by the syndrome of hyperinsulinism." (Harris) (66)

FREQUENCY

Harris, (66) in his article, "Hyperinsulinism, A Definite Disease Entity", makes the following statement, "No doubt hyperinsulinism has existed as long as has diabetes and was not recognized, just as hyperthyroidism, now known to be a frequent disease, for a long time was considered a nervous disorder and was not recognized as a disease of the thyroid. Physicians now practicing medicine can remember when the first cases of appendicitis were recognized and operations performed; and it may be predicted that in the near future hyperinsulinism will become recognized as a comparatively frequent disease which in most cases is amendable to treatment, either by dieting or surgery. A chronological review of the cases of hyperinsulinism in the United States and Canada up to 1931 indicates that hyperinsulinism not only is a frequent con-
dition, but that it may cause a wide range of symptoms which heretofore
have been diagnosed as being due to other causes, but which in reality
are manifestations of insulogenic hypoglycemia. Judging from the number
of cases of hyperinsulinism now being reported by many clinicians and
from blood sugar studies in 3,076 cases, in my series of 6641 adult
patients largely ambulatory with gastro-intestinal and nutritional dis-
orders, it seems probable that hyperinsulinism is almost as frequent as
the opposite secretory disorder of the insulin-forming cells of the pan-
creas, hypoinsulinism. Of the recorded fasting blood sugars on 3,076
patients, 535 were diabetic, 218 showed hypoglycemia of varying degree
and 86 of these showed unmistakable signs of hyperinsulinism."

Sippe and Bostock, (143) in Sidney, Australia say: "In a large
series of cases met with in general medical practice, the percentage of
cases of hypoglycemia was 0.47, and that of diabetes 0.51. Thus it will
be seen that hypoglycemia is practically as common as hyperglycemia."

* * *

Seale Harris (64) was the first to allude to this syndrome in 1924.
It was on the following line of reasoning that led him to believe that
such existed: "We know that hypothyroidism is not the only dysfunction
of the thyroid gland and that there is a hypersecretion of that impor-
tant organ, hyperthyroidism, in which there are certain characteristic
symptoms, i.e., the syndrome called hyperthyroidism. It has been ob-
served that hyperthyroidism sometimes precedes hypothyroidism. It seems
probable that there are other dysfunctions of the islands of Langerhans,
besides hypoinsulinism, and that an excessive formation of insulin may occur. Hyperinsulinism should produce definite results, i.e., a reduction in blood sugar, which, when below a certain limit, about 0.70 mg. percent, brings on characteristic symptoms, now known as the insulin reaction. It also seems probable that a deficiency of the secretion of insulin may follow prolonged excessive work of the islands of Langerhans; just as in other glands, or organs, hypertrophy and hyperactivity may be followed by degeneration, atrophy and loss of function."

Having seen the insulin reaction in diabetic patients Harris realized that he had seen non-diabetic patients who had complained of the same symptoms. The first patient, a physician, who presented symptoms of hyperinsulinism, consulted Harris March 19, 1923, saying that every day about one hour before his noon meal he felt weak, nervous and so hungry that he could not work. He and found that he would get relief from taking candy or a soft drink or from drinking milk, eating fruit, or from eating anything. It was then about an hour before his time for luncheon, and a specimen of blood was obtained for the determination of its sugar content. It was found to be 0.065 percent. On another occasion, May 15, 1923, the same hour, the blood sugar was 0.070. This patient has no other symptoms, except that he had been overweight and had lost about twenty-five pounds. His blood pressure was low, systolic 95, diastolic, 60. A well balanced diet was given him, with instructions to take some food of some kind every three hours. A year later this physician told me that he had been feeling well since he had
been taking food five times a day." Harris (64) After noting this case and several others similar, Harris ran blood sugar determinations on 253 of his patients. Ninety-two were diabetic with hyperglycemia, twelve had blood sugar below .070 percent and all of these with two or three exceptions had symptoms referable to hypoglycemia. To rule out the possibility that these patients may have been starved or had insufficient foods that might have given these results, blood sugar determinations were done on four patients that were literally starving to death. Three were carcinoma of the esophagus with almost complete atresia. Their blood sugar levels were normal, being kept within normal range, according to Harris, by endogenous catabolism. Thus Harris was the first to point to hyperinsulinism as a condition perhaps a disease entity with definite symptoms. Following this introduction of the condition, others soon recognized it.

Jonas (84) in 1924 presented a case of spontaneous hypoglycemia occurring in a diabetic ten days after insulin was discontinued in his treatment. The explanation for it he could not say, but said that a delayed insulin reaction may have been the cause. The patient died but no autopsy findings are given.

John (82) in 1927 presented a case of diabetes which later developed hypoglycemic manifestations. He also gives evidence that after a heavy carbohydrate meal the islands of Langerhans may be overstimulated and throw out too much insulin which would quickly reduce the blood sugar far below normal and give rise to hypoglycemic symptoms. He gives
figures as low as 31 and 36 mg. percent in patients he has studied. Hypoglycemia thought to be due to pancreatic origin then, is presented by Harris, Jonas, and John, but thus far conclusive evidence has not been advanced to support a diagnosis of spontaneous clinical hyperinsulinism.

Wilder, Allan, Power, and Robertson, in 1927 (166), studied both clinically and at necropsy a severe case of spontaneous hypoglycemia. This case was one having a primary carcinoma of the islands of Langerhans, with metastases to the liver and lymph nodes. This case was the first of its kind to be described and in this sense represents a new disease. The patient who was a physician, noticed sudden attacks of weakness, faintness and paresthesias about twenty months before his death; these later became more frequent and more severe, producing profuse sweating and trembling. It was noticed that the attacks could be cured or prevented by eating frequently or by taking sweet drinks. After a year the severity of the attacks was so great that a short fast resulted in coma and it became necessary to watch him while asleep and to give him candy at the first sign of unusual behavior. A complete metabolic study was made of the patient and then an exploratory operation was undertaken, disclosing a tumor mass in the pancreas with metastases in the liver. One month later he died. At necropsy a considerable portion of the pancreas was found replaced by a carcinoma of islet cells with numerous metastases in lymph nodes and the liver. Extracts of the carcinoma in the liver contained insulin. Extracts were also made of non-
cancerous liver tissue and found to be inert; those of the tumor were very active by its power to reduce the blood sugar in rabbits. The explanation of the symptoms in this case was that small amounts of insulin were being liberated constantly whether the blood sugar was high or low, that is irrespective of the need for insulin. The insulino-genic tissue in the liver was released from all influences which ordinarily control the output. They believe that the hyperinsulinism and symptoms of spontaneous hypoglycemia were due to the metastatic tumor tissue rather than that located in the pancreas—the primary site. Further they explain that the glycogen was unusually firmly held in the liver by the constant maintained insulin action and the liver was filled to capacity with glycogen and no longer able to act normally as the reservoir for glycogen. Prior to this work, carcinoma arising from the islands of Langerhans had not been conclusively demonstrated.

The next case markedly similar to this one was reported by Thalhimer and Murphy (151) in 1928. Their case, a white woman age 57, had symptoms of two and one half years duration, finally developing to a state of almost constant semi-stupor accompanied by frequent convulsions and marked hypoglycemia until death followed, apparently from exhaustion. At necropsy a primary carcinoma of the islands was found. The symptoms and hypoglycemia were explained as in Wilder’s et al case by the active secretion of insulin by the tumor cells causing a hyper-insulinism which was responsible for the low blood sugar and death. No extracts were made from the tumor tissue.
Another case of carcinoma of the islands of Langerhans being etiological in production of spontaneous hypoglycemia was reported by Howland, Campbell, Maltby, and Robinson (77) in 1929. This patient was a white woman age 52 that gave a history of six years of symptoms of hypoglycemia climaxing in attacks of coma and convulsions increasing in their frequency, but warded off by the administration of food and found to be caused by low blood sugar levels. A study of the case revealed the erratic response to carbohydrate administration unless suitably administered and led to the diagnosis of the cause as an islet cell tumor of the pancreas. The patient was operated and a tumor of the pancreas was found. No metastatic tumors were found. This patient recovered and became entirely symptom free. This constitutes the first successful treatment of such a case to be found in the literature. This tumor was of the slow growing type of carcinoma. Insulin was extracted from the tumor tissue. Early diagnosis together with the fact that the tumor was slow growing with no metastases were the lifesaving criteria in this case. As in the others the uncontrolled output of insulin by the tumor tissue is given as the cause of the symptoms of spontaneous hypoglycemia.

With carcinoma of the islands of Langerhans established as an etiological factor in the production of spontaneous hypoglycemia due to hyperinsulinism, let us now turn to the benign adenomata as another factor of causation.

R. L. Cecil (30A) in 1911 reported a case of adenoma of the islands of Langerhans and refers to two others by Helmholtz and Nicholl.
symptoms pertaining to hypoglycemia were found in the case histories.

Warren (160), in 1926 published a report on sixteen cases of adenomata of the pancreas which were found only at necropsy. These cases had given no clinical history that could be allayed to the tumors.

The first case of benign adenoma of the islands of Langerhans as the cause of hyperinsulinism was reported by McClunhan and Norris (109) in January, 1929. The patient had typical symptoms of hypoglycemia associated with loss of memory and of consciousness. The patient died and at autopsy was found to have a large circumscribed, beta cell adenoma, composed wholly of island cells. The remaining islands were also found to be hypertrophied. The symptoms of hypoglycemia were explained by the uncontrolled secretion of insulin by the tumor. McClunhan and Norris state that this relationship of hypertrophy and adenoma formation would seem to add further evidence toward the creation of a new disease entity.

Another instance of cure from the symptoms of spontaneous hypoglycemia by removal of an adenoma of the islands of Langerhans is reported by Womack, Gnagi, and Graham (172), in 1931. This patient had periods of confusion for one year. A tentative diagnosis of cerebral tumor had been made and the patient was put on phenobarbital. Investigation of the blood sugar found it below normal for enough to account for the symptoms. At operation the tumor was found at the junction of the body and tail on the peritoneal surface. These writers state that if the tumor is imbeded in the substance of the gland, recognition
would be difficult as well as removal. They also say that any case of hypoglycemia not be called idiopathic till serial sections of the pancreas is done at necropsy to positively rule out adenomata that may easily escape recognition by only a superficial examination.

Smith, and Seibel, (146) 1931 reported five cases of beta cell adenomas of the islet cells of the pancreas. In the first case the periodic attacks of dizziness, loss of consciousness, and coma, with peculiar emotional reactions that this patient experienced were explained only by this functioning tumor of the islands of Langerhans which was found at autopsy. The third occurred in a boy who had typical symptoms of hypoglycemia for one and a half years. The fourth was an incidental finding in a man 50 who died of intestinal obstruction. This patient had been considered mentally defective, because of periods of loss of memory. The fifth, found at autopsy incidentally, in a patient who died of pulmonary embolism.

That a very small tumor of the islands of Langerhans may be responsible for a high degree of hypoglycemia was shown by Rabinovitch, Jacob, and Barden, (133) in 1932. They presented a case of hypoglycemia which was caused by a small adenoma of the islands. They state that the histologic studies justifies the diagnosis. The cells stained like beta cells and are capable of elaborating insulin-like substance as judged from the body reaction in their presence. They feel that the character of this secretion is somewhat different from normal insulin, particularly insofar as it is much more potent. This conclusion they
believe is justifiable if the extreme degree of hypoglycemia that may result from such a small tumor is considered.

Tomkies (155), 1932 also reports a case that was cured of symptoms of hypoglycemia by the surgical removal of an adenoma of the islands of Langerhans.

A benign adenoma of the islands was found by Derick, Newton, Schulz, Bowie, and Pokorney, (43) 1933, with a cure by surgical removal. The symptoms in this case were identical to those found in an overdose of insulin. Up to this time this female patient age 57 was the oldest patient on record in whom a neoplasm of the islands of Langerhans has been found. It is also one of the few cases which the benignity of the tumor was unquestioned.

Carr, Parker, Grove, Fisher, and Larimore, (29) 1931, also reported another instance of a benign adenoma of the islands of Langerhans occurring in a boy 19 years of age. It was stated by Carr et al, that the tumor occurring in Derick's et al case would likely to be malignant in consideration of her age, while their case in a boy of 19, malignancy would not be expected. Derick's case was first thought to be one of neurasthenia until second admission to the hospital when the blood sugar studies were made and the diagnosis of hyperinsulinism made. Evidence that the patient's trouble and symptoms were caused by the tumor are shown by the facts that the tumor itself was found to be rich in insulin, removal resulted in complete cure. The symptoms and blood sugar findings are again explained on the basis of uncontrolled
hypersecretion of insulin by the tumor tissue. Twenty months later the patient was still normal with a blood sugar of 70 mg. percent, and no symptoms, and quite comfortable on three small meals a day. This patient at some times had a blood sugar as low as 25 mg. percent without showing symptoms. The authors say that this case demonstrates very well that there is no critical level of blood sugar at which a patient will develop symptoms.

In an excellent review of the literature on adenoma of the islet cells with hyperinsulinism, Whipple and Frantz (165) in 1935, gathered 157 reported cases of islet tumor. Seventy-five cases of hypoglycemia were ascribed to hyperinsulinism without verification at operation or autopsy. Of the 82 remaining cases of which the pancreas was examined, normal tissue was found in 13, hypertrophy in four, chronic inflammatory change in three, leaving 62 cases of tumor. Fifty percent of these were incidental without hypoglycemia. Thirty-one were associated with hypoglycemia. Of this thirty-one, ten were found at autopsy, twenty-one were found at operation. Of this twenty-one cases four were carcinoma and seventeen were adenomata which were treated by excision and resulting in cure.

Liu, Loucks, Chou, and Chen, (96) in 1936, reported a case with chronic post-absorbtive hypoglycemia associated with coma and convulsive seizures. At operation a tumor of the pancreas was found which was excised. Following the operation, the symptoms of hypoglycemia completely disappeared. Examination of the tumor found it to be com-
posed of islet tissue and yielded more insulin than normal. The hypo-
glycemia was, in a large measure, related to the fact that the comb-
ustion of carbohydrate proceeded at a faster rate and played a more
dominating role in energy metabolism than normal, thus sparing fat and
protein. This action combined with overeating produced obesity in this
patient. Preoperatively, glucose and epinephrine combatted the hypo-
glycemic symptoms satisfactorily.

This I believe is sufficient evidence to prove that an adenomata
of the islands of Langerhans may cause spontaneous hypoglycemia.
However, causes of hyperinsulinism do not stop here, as hypertrophy
and hyperplasia must be considered.

Phillips, (128) in 1931, presented a case which clinically app-
eared to be uremia with low blood sugar estimations and at autopsy
proved to be subacute glomerular nephritis and hypertrophy of the is-
lands of Langerhans. This case was that of a male negro age 56 who was
found in the street unconscious. His wife said that a doctor had told
him he had kidney trouble two weeks before admission to the hospital.
On admission he was in coma; skin cold and clammy. Respirations were
labored and the breath fetid. The examination of the chest showed
rales at the bases. The heart was not enlarged and no murmurs present.
Urine sp. gr. was 1.012, many hyaline casts, no sugar and a cloud of
albumin. Blood urea nitrogen was 133, blood sugar 45 mg. percent.
The patient apparently never regained consciousness. The last blood
sugar done was 25 mg percent. At autopsy a subacute glomerular nephritis
was found. Examination of the pancreas found the islands to be enlarged but not distorted, nor did the cells show degeneration. Certain areas showed that there was definite hyperplasia. The average size of the ten islands measured was 328 by 242 microns; the normal given as 157 by 146 microns. They conclude that this condition was an entirely separate pathologic condition from the subacute glomerular nephritis. The low blood sugar is explained by the increased insulin production by the hyperplastic islands. They believe that hypertrophy of the islands is an explanation for cases of chronic hypoglycemia, which are of long duration, show mild symptoms and are relieved by a high carbohydrate diet. They advance the theory that periods of high sugar intake may invoke a hypertrophy giving rise later to hyperinsulinism and hypoglycemia.

John, (83) in 1931, presented a case of a male aged 61 diabetic which was treated by the usual dietary and insulin. The patient also had evidence of hyperthyroidism which was treated with lugol's solution. The hyperthyroidism disappeared. In six months the insulin was discontinued and the diet was increased, the patient remaining sugar-free. The patient did not gain weight. One year later he was admitted to the hospital in coma. The blood sugar was 30 mg. percent. Despite intravenous dextrose the patient died. The only explanation for the low blood sugar was found at autopsy, where markedly hypertrophied islands of Langerhans was found. The question was brought up by John as to whether it is the hypertrophy of the islands per se which causes hyperinsulinism or is it the regulating mechanism which causes hyperinsulin-
ism or is it the regulating mechanism of the insulogenic output which brings it about, either in the presence of hypertrophy of the islands or when the islands are normal; hyperinsulinism being seen in both instances.

Hypertrophy of the islands was also observed by Mosenthal, Ashe, Poindexter, and MacBrayer, (118) in 1933. They had the unusual opportunity to observe a case of essential hypertension from its beginning to termination, a duration of thirteen years. This patient had symptoms of hypoglycemia for nine years, increasing in severity, and finally became so marked that they certainly favored, if they did not cause, death. At autopsy the pancreas showed hypertrophy of the islands. The average diameter of the measured islets being 215 micra. They state that this is about 75 micra greater than the accepted normal size.

These authors put the cause of the low blood sugar of this patient, which at times went as low as 50 mg. percent, entirely on the hypertrophy of the islet tissue resulting in hypersecretion and hyperinsulinism. This patient had hypoglycemic reactions at comparatively high levels namely 61 mg. percent. These authors state that the individual reaction to the blood sugar concentration plays a very big role and that it must be given due consideration in every instance. This case showed that the blood pressure rises markedly as the blood sugar drops, and according to Dr. Ashe this finding is of great value in a differential diagnosis in comatose patients between insulin overdosage and hypoglycemia on one hand, and other conditions associated with unconsciousness.

As John (83) stated, these authors agree that a large constant supply
of carbohydrate food over a fairly long period of time might result in
hypertrophy of the islands of Langerhans. Under these circumstances if
the carbohydrate intake is suddenly decreased an excess insulin supply
resulting in hypoglycemia, may be expected.

The case of adenoma of the islands already mentioned by McClanahan
and Norris (109), also had hypertrophied islands in the neighborhood of
the adenoma and it is possible that the excess insulin supply could
well have come from these in part.

Hypertrophy of the islands of Langerhans has been noted in the child
of a diabetic mother.

The complete sequence of events was noted for the first time by
Gray and Feemster, (61) in 1926. This case was one of a child born of
a diabetic mother whose disease had received inadequate attention. During
the course of the pregnancy it was found that the mother needed less
insulin. At the fourth month on a diet of 1800 calories, 30 units of
insulin was given, and there was fourteen grams of sugar excreted daily.
At the eighth month the diet was 2235 calories with only 15 units of in-
sulin given, and there was no excretion in the urine. This increased
tolerance is consistent with the finding of Joslin, (89) in 1923, when
he noted the increased carbohydrate utilization on the part of diabetic
mothers in the last months of pregnancy. The infant born prematurely
was found to have a blood sugar of 67 mg. percent on the third day, the
infant dying on the fourth day. The blood sugar of the mother rose from
96 to 225 mg. percent post partum. The mother also died and necropsy
failed to reveal satisfactory cause for her death. Necropsy of the infant revealed a hypertrophy and hyperplasia of the islands. There was three times as many islands as found in a normal pancreas and eight times the size of normal ones. Thus there was a twenty-four fold increase in islet tissue. This hypertrophy and hyperplasia was considered to be a compensatory phenomena; the hyperglycemia in the mother bringing about a response of the pancreas in the fetus. At birth the blood sugar of the mother was withdrawn, and in the presence of an oversupply of insulin by the infants pancreas, the blood sugar of the infant was utilized in an increased amount resulting in severe hypoglycemia.

Hypertrophy of the cells of the medulla of the suprarenal glands with hemorrhage and necrosis was also found, this being explained by the compensatory antagonistic hypertrophy of them to combat the islet secretion. Gray and Feemster conclude that the hypoglycemia played the role in causing the sudden death of the baby. These authors state that the infrequency of observations such as this are attributed to the tendency to sterility and to the practice of therapeutie abortion of diabetics.

Three cases of fetal death one intrauterine and two shortly after delivery were presented by Gordon, (56) in 1935. He states that a diabetic mother is frequently delivered of a dead fetus; or, if it lives, it dies soon after birth. The full term fetus of the diabetic mother is usually large. The first case was one of a diabetic mother who was eight months pregnant. This patient noted the cessation of fetal movements twenty-four hours before she went into coma in which she died.
The second case was born by caesarian and found to have a blood sugar of 45 mg. percent. The baby lived about 12 hours. The third case was a diabetic mother that had had multiple miscarriages and three full term large dead fetuses. The last pregnancy was delivered by caesarian, but this baby also only lived 12 hours. Study of the autopsies was enlightening. All babies were of large size. The pancreatic tissue from all the babies showed an enormous hypertrophy and hyperplasia of the insular tissue. The individual cells were large and marked increase in number, resulting in an increase in island size, in some instances as much as six to eight times the average diameter in the normal newborn pancreas. In some sections of the pancreas approximately 50 percent of the tissue was insular tissue. Around the islands was a dense infiltration of eosinophiles. The livers showed extreme grade of erythropoiesis, suggesting a myeloid change. This author finds that, "in a study of a large number of diabetic mothers, it is noted that the diabetic condition in these mothers is improved from the second to the seventh month of their pregnancy. In order for the severe diabetic mother to metabolize the increased amount of carbohydrate ingested, it is necessary that there be more insulin present than the mother can supply. It is reasonable to assume that this increased supply of insulin is derived from the pancreas of the fetus, or that the fetus metabolizes the surplus carbohydrates with the insulin it produces. By reason of this fact, there is a greater supply of carbohydrates to the fetus than normally. This would account very logically for the increased size of the fetus at term."
Because of this increased supply of carbohydrates to the fetus or the increased demand on the part of the mother for insulin, there results a demand hypertrophy and hyperplasia of the pancreatic tissue."

"As the fetus continues to grow in utero, the pancreas is able to secrete more and more insulin, and capable of metabolizing larger amounts of carbohydrates. As the supply of carbohydrate is diminished in proportion to the increasing supply of insulin, relatively, the fetus begins to suffer a greater danger—-that of hyperinsulinism. This is substantiated by the extremely low blood sugars reported to be present in the blood taken from the heart at post mortem examination." Gordon states that as early as 1911 Carlson and Drenan took bitches who were pregnant, and removed the pancreas. They found that in these dogs the diabetes was better during the pregnancy, and concluded that this was due to the increased insulin given by the fetal pancreas of the puppies in utero. Gordon concludes that the cause of fetal death in the diabetic mother is due to hypoglycemia resulting from hyperinsulinism.

With spontaneous hypoglycemia being caused by hypertrophy and hyperplasia of the islands established, we find that it is also thought to be caused by hyperfunction of normal islands.

Finney and Finney, (47) of Baltimore in 1928, reported the successful resection of a large portion of a normal appearing pancreas for hyperinsulinism. This case was that of a white widow age 53. She was referred to Finney and Finney jr., by Drs. T. P. Sprunt, and L. F. Barker, who found she had hypoglycemia with blood sugar readings as low
as 40 mg percent when fasting. The patient had complained of having had at varying intervals for four years of spells of confusion with mental lapses and strange behavior. It is interesting that the first attack came coincident with the menopause. At first she only noticed that she could not think clearly or concentrate. She had double vision at times. These spells became more frequent and prolonged. The spells usually came on before breakfast. Any alarm or trouble precipitated attacks and she fell many times. The symptoms became worse and finally were occurring every day. While under observation attacks were prevented and aborted by giving of food. Fasting blood sugar was found to be 52 mg. percent. The similarity of the case to that of Dr. Wilder et al (166) prompted the Finneys to investigate the pancreas surgically. They operated on the patient with the intention, after examination of the pancreas, of partially resecting it. The pancreas was found to be normal and two thirds of it was removed. Microscopic examination of the pancreas found the pancreatic structure apparently normal with no demonstrable change in the islands of Langerhans. Blood sugar readings have been higher since the operation, but the patient continued to have some attacks which were thought to be psychogenic in character. The finding of the normal pancreas in this case resulted in the conclusion that the hyperinsulinism and consequent hypoglycemia was on a functional basis.

Winans, (169) of Dallas, Texas, at the meeting of the Southern medical association, in November, 1929, reported three patients having symptoms associated with hypoglycemia, in whom he thought he could
exclude any other endocrine disturbance except an excessive secretion of insulin by the islet cells of the pancreas. The three of Winans's cases gave a history of having lived on a high carbohydrate diet, which he thought was the exciting cause of the hyperinsulinism, with the resulting hypoglycemia. The important symptoms of the first case were, severe headaches and inability to concentrate at about 4:00 P. M. His blood sugar was low during an attack, .073 percent. The complaint of the second, who was an obese woman, was weakness, trembling, and inability to keep from crying. She had been dieting to reduce. Her blood sugar during an attack was .059 percent. The third case, an overweight woman, age thirty, complained of attacks of weakness, dizziness, pain in the pit of the stomach and extreme hunger, before lunch and in the middle of the afternoon. Her blood sugar in the P. M. was .067 percent. According to Winans his patients did best on a balanced diet with regular systematic exercise. He concluded by saying, "Obesity, presumably from overeating precedes diabetes. As long as the pancreas can respond to the overstimulation of excess diet, they are in the class of chronic hypoglycemia (hyperinsulinism) ".

Hyperinsulinism of functional, or nervous origin was studied by Hoxie and Lisherness, (78) of Kansas City. They attacked the problem of hyperinsulinism and hypoglycemia by studying records of routine blood sugar tolerance tests, and whenever low blood sugars were observed, noting the symptomatology of the patients. Three hundred seven routine studies were made, 95 had a fasting blood sugar below .070 percent.
In 23 cases, when blood sugar was below .070 percent, there was sugar in the urine, suggesting the independence of blood sugar level and glycosuria. They concluded that hypoglycemia may become chronic and that it is accompanied by mental and nervous disturbances similar to those produced by hyperinsulinism and hypoglycemia. They believe that their cases were of functional or nervous origin, suggesting a lowered sugar metabolism of the body, more than hyperinsulinism. They consider the underlying cause to be some type of exhaustion, and in their cases found that with returning strength the blood sugar returned to normal limits so they aren't quite clear whether the hypoglycemia caused the nervousness or the nervousness caused the hypoglycemia.

Nielsen and Eggleston, (123) in 1930, reported three cases of functional dysinsulinism seizures. Their first case in three years had had eleven attacks of complete unconsciousness with more than fifty attacks of petit mal. The blood sugar readings were as low as .050 percent. Frequent meals and supra renal gland relieved the patient. Another patient had fainting spells and was relieved by adrenalin and supra-renal gland by mouth. The third case, a man age 23, had more than 125 attacks of grand mal in 13 years, all before breakfast. The blood sugar was .064 percent. Orange juice before breakfast gave relief from attacks. Their cases also suggest an adrenal deficiency associated with hyperinsulinism.

Waters, (161) in 1931, in discussing the role of diet in the etiology and treatment of spontaneous hypoglycemia, said that there is
evidence that a prolonged high carbohydrate diet stimulates excessive insulin formation which results in spontaneous hypoglycemia, apparently on a functional compensatory basis. He supports his contention by presenting three cases of spontaneous hypoglycemia who had previously had high carbohydrate diets. He treated them with high fat diets and the patients had no more symptoms.

Gammon and Tenery, (50) in 1931, reported a case which they designated as being of the dysinsulinism type. This patient a woman age 39, complained of attacks of weakness and unconsciousness with muscular twitchings. She had attacks of unconsciousness repeatedly and finally found that taking of food would abort an attack. The case was diagnosed once as a reaction of "nerves", which distressed her very much. There was some temporary disturbance in the menses. Finally a diagnosis of hypoglycemia was made. Her blood sugar at times was as low as 45 mg. percent. The patient was placed on a high carbohydrate diet and frequent feedings between meals and at bed-time. She had no recurrence for one year and has been perfectly well. This patient's symptoms dated back to 1928, which ruled against the condition being neoplastic.

Brougher, (19) in 1934, also found hypoglycemia occurring in some of his patients which he could not explain on the basis of a motor or secretory disturbance of the gastro-intestinal tract. Glucose tolerance tests were made on the patients and a insulinogenic disorder noted. Fourteen cases of irritable colon had hypoglycemia as chief complaint. Their fasting blood sugars were from 40 to 122 mg. percent. No glycos-
uria was found in the glucose tolerance tests. The diets of the patients were low in starch and fat so as to not excite hypersecretion of insulin. These cases were declared functional on this basis.

Love, (98) in 1933, had cases of ulcerative colitis with symptoms of hypoglycemia. On taking glucose tolerance curves some were found to have diabetic curves. He therefore called it dysinsulinism. Love states that whether or not a case is one of hyperinsulinism or dysinsulinism, depends on the response to the dextrose tolerance test and on the presence of transient hyperglycemia and glycosuria. Like Brougher some of his cases were put on a functional basis.

Winans, (170) in 1933 reported a case of hypoglycemia convulsions in which at operation the pancreas was found to be only one third normal size. Microscopically the pancreas was found to be normal both in respect to the islands and acini. The overproduction of insulin, as suggested by John was considered, but this patient's glucose was increased and she gained weight subsequently. No endocrine basis could be found. Tumor of the pancreas wasn't entirely excluded, but there was no indication of one. He then considered that there was a disturbance in the balance between the external and internal secretion of the pancreas. Epstein and Rosenthal, (46), in 1925, found that the passage of trypsin into the blood stream of the pancreas neutralizes insulin and by passing into the portal circulation causes glycogenolysis with a consequent hyperglycemia. They concluded that no definite barrier exists between the structures which produce internal secretion and those concer-
ned with the external secretion of the pancreas. The possibility that the internal blow of trypsin may be a part of the mechanism which regulates the supply and activity of the internal secretion of the pancreas is indicated. They also say that inactivation of insulin by trypsin may occur within the body of an animal under suitable conditions. Winans advances the idea that the small pancreas in this patient contained sufficient tissue capable of secreting a relatively normal amount of insulin. If ligation of the pancreas, obstruction of the duct, or other disturbances which cause atrophy of the acini may be assumed to act in some instances, by removing the inhibiting effect of acinar secretion, as shown by Epstein and Rosenthal, it seems possible that the reduced amount of externally secreting tissue may have failed to provide an inhibiting effect upon the insulin. He further states that if this hypothesis is adopted it is not necessary to assume that there was either overproduction of insulin, or a release of abnormal insulin, in this case. Another case of hyperinsulinism is postulated; this case I believe could be placed in the category of functional hyperinsulinism.

It is thus shown by the works of these men that spontaneous hypoglycemia can occur because of hyperinsulinism, which may be due to a malignant neoplasm of the islands, adenoma, hypertrophy, or hyperfunction. All the cases reported in the literature, of course, have not been mentioned, only those that I considered scientifically worked up, and showed definite proof of their etiology were given. I believe the works of the most prominent men in this field have been presented.
The relationship of the pituitary gland to carbohydrate metabolism has probably best been investigated by Houssay and Biasotti, from 1924 to 1930 (76). Their investigations have shown that the pituitary gland is one of the most important endocrine factors in the regulation of carbohydrate metabolism. They found that in dogs after hypophysectomy, some of the animals tended to have severe hypoglycemic crises. When the blood sugar remained for some time at .070 per cent or below, symptoms appear; general weakness, postural instability, the animal falls, abundant secretion of saliva, tendency to opisthotonus, convulsions that may become violent, coma, lowering of body temperature and death occurs. If given soon enough, intravenous glucose brought about complete recovery from the symptoms.

They found that injections of insulin in these dogs had a high mortality. Hypoglycemia was produced more easily and was less well tolerated. The dose that ordinarily doesn't produce symptoms in a normal animal does produce them in the hypophysectomized animal. They state that up to this time the anterior lobe of the pituitary gland hasn't been known to act against insulin. In their experiments they found that the anterior lobe has predominate, perhaps exclusive control of carbohydrate metabolism as far as the pituitary gland is concerned. The posterior lobe was shown also to be antagonistic to the action of insulin, but to a lesser degree. The principal arguments in favor of a predominate, if not exclusive, role played by the anterior lobe of the pituitary in carbohydrate metabolism are two according to Houssay.
and Baisotti they are: (1). Frequent occurrence of diabetes in acromegaly, in which disease there is an acidophile adenoma of the anterior lobe.  (2). Implantation of the anterior lobe in the hypophysectomized toad protects against hypersensitiveness to insulin and reestablishes diabetes after pancreatectomy. The posterior lobe is less active in this respect.

From experimental evidence the importance of the pituitary on carbohydrate metabolism is made clear by Houssay and Baisotti: (1). In hypophysectomized animals hypoglycemia occurs more readily and is less well tolerated, therefore there is greater sensitiveness to insulin.  (2). Pancreatic diabetes (dog and toad) and phlorhizin diabetes (dog) are much less severe.  (3). Glycosuria is less marked after pancreatectomy or phlorhizin injection.  (4). Sugar may be metabolized after pancreatectomy (increased R. Q. and partial retention after sugar ingestion). They believe that the action may be direct on the tissues or indirect through the pancreas, liver or nervous system. An indirect action might be carried out by the regulation of insulin secretion or neutralization of its effects. They believe further study will reveal more information regarding the interrelationship. Collip, in 1935 (33), corroborated the work of Houssay. To review his report would be essentially repetition.

Burn, in 1923 (21), believed that there were two observations regarding the relationship of the pituitary gland to carbohydrate metabolism that were authentic, namely, (1). The posterior lobe is antagon-
istic to insulin, and, (2). The diminution of posterior lobe secretion either experimentally or clinically results in high tolerance for sugars.

Looking back to our history we see that Cushing, (39) in 1912 (p.132), was the first to call attention to hypoglycemia in hypopituitary conditions. Cushing said that the degree of hypopituitarism may be determined by estimation of sugar content of the blood rather than the more tedious production of alimentary glycosuria through feeding tests. In his book of 1912 he refers to 13 patients with existent hypopituitarism, who showed epileptiform tendencies. He also noted that he had never noted these in hyperpituitarism. He again in 1930 (40), said that clinically the syndrome supposed to result from insufficiency of the anterior lobe is accompanied by high tolerance for carbohydrate. In 1933 Cushing further stated, (41) that the high tolerance for carbohydrate in hypopituitary states is due to an increase of the insulin content of the blood due to the withdrawal of the counter-active posterior lobe principle.

J. Wilder, as cited by Wauchope (162), and Gammon (50), in 1930 published two cases of spontaneous hypoglycemia in which there were radiological and clinical signs of pituitary tumor. He presented the condition as a new syndrome, pituitary spontaneous hypoglycemia, and considered it to be due to lack of the secretion of the anterior pituitary leading to relative hyperinsulinism. Wilder also quotes four cases of spontaneous hypoglycemia associated with proved destruction of the
anterior lobe of the pituitary. "J. Wilder's first patient, (162) (p. 135-136), was a stout woman of 45 who had periods of semi-consciousness lasting for twelve to 24 hours. Sometimes she would stare vacantly with open eyes, but with no conscious response; restlessness and difficulties in speech occurred in the morning. Babinski's sign was positive on both sides in an attack and the systolic blood pressure was low (95-100); the fasting blood sugar was found to be .020 per cent, and intravenous dextrose cut short an attack at once. The chief signs of pituitary involvement were obesity, intense headaches, and enlargement of the sella turcica.

His second patient was also a woman age 55 years, who had left off eating sugar for three years because she was getting stout; she began to have attacks of odd behavior before the midday meal, especially if it were late; she seemed in a dream and called to a dead sister; sometimes she had twitching of limbs and became semi-conscious. Her fasting blood sugar was .061 and .045 per cent. Sugar relieved symptoms. She was obese; the x-ray picture suggested a tumor in the sella turcica and there was blurring at the edges of the optic discs."

Goldzieher, in 1936 (54), reported 112 cases of hypoglycemia, 88 of which showed hypopituitarism. The hypopituitary group was the largest and included one case of Simmonds disease, one diagnosed as basophile adenoma, 14 cases of adiposo-genital dystrophy, while the others were characterized by the typical fat distribution, postural hypotension, inadequate rise of the metabolic rate after a protein meal, typical blood
picture and dysplasia of the cranium on x-ray examination. These patients were given injections of fresh anterior lobe extract. Hypoglycemic symptoms disappeared gradually within a few weeks during the course of treatment. With reference to Houssay's and Collip's work, Goldzieher states that if it is permissible to draw any analogy from experiments to human pathology, it is fair to assume that functional deficiency of the anterior lobe of the hypophysis affects carbohydrate metabolism in the sense of lowering the fasting blood sugar, increasing insulin sensitivity and decreasing the response to other endocrine factors (adrenal, thyroid) which constitute important links in the chain of endocrine regulations. Goldzieher emphasizes the significance of pituitary and thyroid insufficiency in the pathogenesis of hypoglycemia, stating further that hyperinsulinism is relatively rare that the organic background should be looked for in the thyroid and pituitary glands.

A. S. Blumgarten, (14) reported a case of dyspituitarism in which spontaneous hypoglycemia developed. This patient was a 19 year old female. Obesity was her chief complaint. She was given thyroid extract and put on a diet. She lost weight, but began to suffer from attacks of weakness and loss of memory. These attacks were relieved by eating large amounts of carbohydrate. Her basal metabolism was minus 17 per cent, fasting blood sugar was .080 per cent at one time of symptoms it was .060 per cent. The obesity was the pituitary stigmata in this case. Blumgarten believes that the low carbohydrate diet and
thyroid extract caused the attacks of hypoglycemia. He believes that it was the dyspituitarism that was responsible for the attacks by making the patient more sensitive to the normal insulin secretion; the thyroid extract given further increasing this sensitivity resulting in hypoglycemia symptoms.

Wolf, 1937 (171)(p. 45), in his book, "Endocrinology in Modern Practice", says that the insulin-antagonizing hormone is probably secreted by the eosinophilic cells of the anterior pituitary gland, that it acts on the supposed sugar center of the brain, which in turn acts on the adrenals and sympathetic nervous system. Absence of the hormone results in marked, at times fatal hypoglycemia, in an increased sensitivity to insulin and diminution of the glycogen reserves. He states that these findings are corroborated by the high fasting blood sugar which has been observed in acromegaly, the frequent occurrence of diabetes in acromegalic individuals, and the hypoglycemic attacks seen in hypopituitarism. Patients with hypopituitarism are extremely sensitive to insulin, since their blood sugar is already low as a result of the pituitary deficiency; insulin reduces it still further, producing insulin shock quite readily. Fröhlich's syndrome, Dercum's disease, and Simmonds disease are listed as anterior pituitary deficiencies, as well as certain forms of infantilism mongolism and dwarfism. Speaking of Fröhlich's syndrome, (p. 72) he states that there is an increased tolerance for carbohydrates resulting in low values of blood sugar which remains almost unchanged when amounts of 200 to 400 grams of sugar are
ingested.

With the physiology of the pituitary in relation to carbohydrate metabolism quite established, it is then generally agreed that hypofunction of this gland will lead to symptoms of spontaneous hypoglycemia in certain cases.
Wolf, 1937 (171)(p.309), in discussing the physiology of the adrenal cortex says that, "the regulation of carbohydrate metabolism by the cortex is indicated by the depression of the blood sugar level and increased sensitivity to insulin seen in Addison's disease." The mechanism is not given. In his discussion on the physiology of the medulla of the adrenal in relation to metabolism he says that adrenalin, the principal secretion of the medulla, (p. 316), "is a general stimulant for all protoplasmic activities of the cells, unless inhibited by its antagonists as vagus, pituitrin and insulin. Subcutaneous injection of adrenalin causes an increase in blood sugar which may last several hours. Sometimes the sugar spills over into the urine, producing glycosuria. The liver glycogen is converted into glucose while the non-liver glycogen (chiefly derived from the muscles) diminishes in quantity. At the same time the blood lactic acid is increased, indicating a cycle which is taking place. There is a conversion of liver glycogen into glucose, which is pulled into the blood stream whence it is transferred into the muscles and this in turn changes to lactic acid which the liver again converts into glycogen." In discussing general hypofunction of the adrenal glands, (p.320) he states that the blood sugar is low and there is a high sugar tolerance.

Biery and Malloizel, in 1908, as cited by Pemberton, 1925 (126), found that complete removal of the adrenal glands produced hypoglycemia.

Forges, in 1910, as cited by Longcope, 1928 (97), first drew attention to the occurrence of hypoglycemia in Addison's disease in which
blood sugars were, .052, .033, and .067 per cent. He found also that extirpation of both suprarenals of the dog was followed by hypoglycemia. From this he concluded that the muscular weakness and asthenia of Addison's disease were dependent on the hypoglycemia. Janney, 1918 (81), also reports cases of hypoglycemia occurring in Addison's disease.

Mac Lean and Sullivan, 1926 (99), in studying blood sugar in cases of status thymicolympathicus found definitely low blood sugars. Three cases are presented that before death had blood sugar levels of 42, 52, and 57 mg. per cent. These cases had convulsions. These authors feel that acute suprarenal insufficiency is the immediate cause of death. They point out that the adrenals are frequently found hypoplastic and also there is a frequent association of status thymicolympathicus to Addison's disease. These authors refer to Hedinger and Hart in the German literature as establishing the association of thymic enlargement with diseased suprarenals. Shock, anesthesia, or mild infection is often the discernable cause of status death. A case of suprarenal hemorrhage is given. The blood sugar at death was 25 mg. percent. They further state that if hypoglycemia should be a constant finding it suggests acute suprarenal insufficiency and adequately explains the sudden death in status thymicolympathicus.

Greenwald and Eliasberg, 1926 (62), in discussing the pathogenesis of death from burns, present two cases of fatal severe first degree burns in children. The first case was one of a child two years old. This patient had clonic seizures and acetone breath. Death occ-
urred 36 hours after the burn took place. The blood sugar taken before
death showed it to be absent. The second case, age three, was treated
five days before hospitalization. Examination showed acetone breath,
Kussmaul respiration, and muscle twitchings. Blood sugar immediately
after death was 30 mg. per cent.

They found by animal experimentation that in the first 24 hours
the blood sugar is high in cases of burns; in the second 24 hours the
hypoglycemia is manifest. They believe that in the beginning there is
a hypersecretion of adrenalin, then with the absorption of toxins from
the burn there is degeneration of the adrenals giving rise to insuffici­
cy and consequent hypoglycemia due to failure of adrenalin to mob­
ilize the sugar of the liver.

The first case of carcinoma of the suprarenal gland with a fatal
hypoglycemia was reported in 1930 by H. B. Anderson, (4). This oc­
curred in a man age 33. Four months before death he suffered loss of
speech, this progressed to tiredness and double vision and finally only
semi-consciousness. Glucose intravenously helped only slightly, adren­
alin was also used to no avail. The blood sugar got as low as 40 mg.
per cent. Autopsy showed the left suprarenal nearly destroyed by a
carcinoma of the cortex. The right was fibrotic and small. This patient
evidently died of suprarenal insufficiency. He believes that it is
possible that lowered synthesis of epinephrine failed to liberate gly­
cogen from storage depots.

Rabinovitch, Jacob, and Barden, in 1932 (133), reported a case of
hypoglycemia which at autopsy showed the adrenal medulla replaced by lymphoid tissue. This is the first case found with a lymphoid replacement. They believe it may represent a local manifestation of lymphoid dyscrasia. The blood sugar in this patient was as low as 25 mg. per cent.

The symptoms of cyanosis, choking, dyspnea, stridor, asthma, projectile vomiting and sudden death in infants was studied by Aldrich and Munns, in 1931 (2). They say that these symptoms are found at the time when the suprarenals are undergoing marked involution soon after birth. The blood sugars on 19 infants averaged 60 mg. per cent. It is considered that both hypoglycemia and the symptoms can be explained on the basis of either suprarenal insufficiency with resulting decreased sympathetic activity or of vagotonia. The results are in keeping with the theory that suprarenal insufficiency is the primary cause of symptoms.

J. C. Norris in 1935 (124), reported three cases of hypoglycemia in adrenal disease. The first had an atrophic adrenal disease associated with hepatitis, the second had acute and chronic hepatitis with albuminous precipitate and fibrous adrenals, the third had tuberculosis of the adrenals. All cases had severe spontaneous hypoglycemia attacks. He also states that he has found hemorrhages into adrenals in cases of sudden death.

That hypoglycemia occurs in Addison's disease is quite well established. As has been stated, Forges first described it in three
cases in 1910. Rowntree, in 1925 (136), by his studies in Addison's disease noted frequent finding of a fasting blood sugar below normal. Chapman, in 1926 (31), noted a case with a flat glucose tolerance curve. Welty and Robertson, in 1936 (164), present two cases of Addison's disease in which hypoglycemia was the outstanding manifestation, causing coma subsequently relieved by dextrose. The destruction of the medulla of the adrenals was the cause. They found the glucose tolerance curve to be relatively flat.

Briggs and Oerting, in 1936 (16), reported a case of hypoglycemia in which the blood sugar was 40 mg. per cent, going to 32 mg. percent before death. Delusions and disorientation were present. At necropsy complete atrophy of the adrenals was found. There was a replacement by fat. They believed that this adrenal atrophy was the only cause of the spontaneous hypoglycemia in this case.

These cases, I believe definitely prove that adrenal disease and deficiency, is a cause of spontaneous hypoglycemia.
The relationship of the thyroid to blood sugar and carbohydrate metabolism has been briefly discussed in the section on physiology. First hyperthyroidism will be considered.

"The carbohydrate metabolism is interestingly altered by increased thyroid function. It is well known that cases of hyperthyroidism easily develop hyperglycemia and a spilling over of glucose into the urine, producing glycosuria. The thyroid, by way of adrenalin, mobilizes large amounts of glycogen from the liver, reducing the storage capacity of this organ and muscle tissues. Biologically, this may be explained by the fact that in a hyperthyroid individual who is in a constant state of fright and potential flight, there is an increased muscle activity (as evidenced by tremor and other useless movements). The adrenal medulla, being the organ for emergencies, keeps the muscles in a state of constant tension, which in turn necessitates the presence of large quantities of glucose in the blood and muscles, to supply the needed energy. The exophthalmos in hyperthyroidism, which is an expression of constant fright, substantiates this theory. This constant overmobilization of sugar eventually results in derangements of other glands, notably the islands of Langerhans, pituitary, and adrenals.

If thyroxin and adrenalin increase the blood sugar tolerance, it is clear that they are antagonistic to insulin. This antagonism is therefore not surprising to find that a dose of insulin, which makes the urine of a diabetic sugar free, will fail to do so if thyroid extract and adrenalin are given simultaneously. Also, if a dose of insulin is
so great as to produce insulin shock, the shock can be prevented if thyroid extract is administered at the same time. However, this holds true only as long as there is sufficient storage of glycogen in the liver which can be liberated. After complete exhaustion of the liver glycogen and the blood sugar, further administration of insulin will quickly produce a fatal insulin shock because then there is no more glycogen to be drawn into the circulation for tissue activity." (171, p. 225)

Holman in 1923, (73) reported a case of exophthalmic goiter which following operation developed symptoms of hypoglycemia, most marked of which was restlessness, weakness and shallow rapid breathing. The blood sugar was .048 per cent. His explanation for this was that at operation the trauma throws an excess thyroid secretion into the system. This gives rise to a great rise in blood sugar. This exhausts the supply of the liver. In favorable cases this is replenished, but some cases do not respond and radical treatment is necessary. Their case responded beautifully to intravenous glucose.

John, in 1931 (83) reported that hyperglycemia occurs in hyperthyroidism. He found that thyroidectomy lowers the total metabolism and in consequence improves carbohydrate tolerance. No mention is made of hypoglycemia occurring in the hypothyroid state. In his series of 100 patients 66 percent had impaired carbohydrate tolerance. The renal threshold was also lowered.

From this discussion it can be seen that in hyperthyroidism, hypoglycemia may occur only in certain cases where the blood sugar is ex-
hausted as well as the body storage depots which fail to replenish the
blood sugar. These cases do not respond and manifest the symptoms of
the ensuing low blood sugar.

In the opposite condition of the thyroid gland namely hypothyroidism, we see again a disturbance in carbohydrate metabolism.

Janney and Isaacson, in 1918 (81) in their experiments on dogs, they found that by removing the thyroid gland a marked hypoglycemia appeared in every case. The average decrease being 26 mg. per cent. They also found that the blood sugar tolerance curves were flattened and prolonged. A cretin under their treatment was found to have a blood sugar of 65 to 70 mg. per cent, which became normal under thyroid medication. They concluded that their experiments on dogs prove that hypoglycemia results from hypo-endocrine function as hypoglycemia regularly developed following thyroidectomy in dogs. Explanation is thus afforded for the low blood sugar value observed in myxedema and cretinism. They speculate that the effect of the thyroid is on the liver; the exact mechanism not known.

In treating cases of myxedema, Campbell, (27) in 1929, found that the cases showed a low fasting blood sugar, a high tolerance for sugar as determined by sugar tolerance tests, with absence of sugar in the urine. His case was that of a woman, age 23, who following a thyroidectomy for toxic thyroid, developed myxedema. She gained 40 pounds, thick dry skin, hair dry and brittle, tongue thick, voice a little husky, mentally sluggish and slow to respond. Basal Metabolic rate was
minus 37. Fasting blood sugar was .041 mg. per cent, with an increased tolerance. This fairly advanced case responded and showed marked improvement with thyroid extract. Four other cases of hypothyroidism are presented with B. M. Rs minus 27, 31, 30, and 32, with fasting blood sugars of .051, .051, .037, and .061 respectively. All showed improvement with thyroid extract. As the B. M. R. rose to normal so did the blood sugars. From the case histories no symptoms of hypoglycemic attacks could be found. This author believes that the blood sugar findings may be used as an aid in the diagnosis, and in controlling the treatment of myxedema.

Not all investigators have found this to be true, however. H. Gray, (60) in 1925, observed normal values for sugar during fasting and also tolerance curves were high and sustained.

Gardiner-Hill, Brett, and Smith, (51) in 1925, found in 15 myxedematous persons the blood sugar values during fasting to be normal and their tolerance curves were higher and more sustained. Giving thyroid extracts in their cases brought tolerance curves down to normal. They conclude that certain myxedematous patients may exhibit hypoglycemia but the degree is not great and is usually not responsible for symptoms.

Gammon and Tenery, (50) in 1931, from examination of the literature, say that the evidence as to existence and degree of hypoglycemia in hypothyroidism is controversial. Further, Abrams and Gilligan, (1) in 1934, reported that the fasting serum sugar concentrations and the glucose tolerance curves are normal in non-diabetic patients with hypothyroidism
induced by total ablation of the thyroid gland. As compared with the values observed before thyroidectomy, the fasting serum sugar concentration tended to be slightly decreased and the glucose tolerance tended to be slightly increased after hypothyroidism developed. They also studied the sensitivity to insulin in non-diabetic, non-hyperthyroid patients before and after the development of hypothyroidism induced by total ablation of the thyroid gland. No appreciable difference was found in the average maximum decrease of blood sugar following the subcutaneous injection of 20 units of insulin before and after hypothyroidism developed. Signs and symptoms of mild hyperinsulinism were manifest in patients with hypothyroidism at the same level of blood sugar as in patients with normal metabolic rates. They believe that their results indicate that the response of the sympathico-adrenal system to insulin is normal in these patients with hypothyroidism, and that there is no antagonism between the internal secretions of the normal thyroid gland and of the pancreas.

More recently Goldzieher, (54) in 1936, presented a series of 112 cases with the symptoms of hypoglycemia. Twenty of these were hypothyroids. Most of these cases improved on thyroid medication. He states that the evidence of thyroid influence upon the blood sugar is less clearly established, but still convincing. Higher blood sugar readings and decreased sugar tolerance have been noted in hyperthyroidism, and the opposite has been shown after thyroidectomy (he gives reference to the German literature). Further he states that the administration of thyroid
hormone mobilizes glycogen from its depots, especially from the liver, hence the frequency of liver damage in hyperthyroidism. He says (p91), "It is no contradiction that the liver glycogen is also low in the thyroidectomized animal and in myxedema, partly because of liver damage and partly because of inadequate resorption and utilization of the ingested carbohydrates in hypothyroidism." He further states that the hyperproduction of insulin is only one of the rare causes of hypoglycemia, because the incidence of tumors of the pancreatic islands is small, and failure of intervention of surgery in absence of tumors; hyperinsulinism being only relative in the majority of the hypoglycemic conditions the organic background of which should be looked for in the pituitary or thyroid, and not in the pancreas.

Wolf, (171) in discussing myxedema and cretinism states that there is an increased sugar tolerance.

From this discussion we see that spontaneous hypoglycemia may occur with either hyperthyroidism or hypothyroidism, also that some investigators have failed to note this. From the evidence presented and the explained physiology, that hypoglycemia occurs in hypo and hyperthyroidism can hardly be denied. Further study will no doubt clear up these discrepancies.
Longcope, (97) reported hypoglycemic attacks in a man with scleroderma, who had bronzed skin, hypotension and low basal metabolic rate. He drew attention to similarity to Addison's disease. Thyroid extract improved the scleroderma and elevated the metabolism, but had no effect on the blood sugar or the hypoglycemic attacks.

Gammon, (50) cites Stenstrom, in the German literature who described a young woman, amenorrheic, without axillary or pubic hair and with scant eyebrows, who suffered a single attack of hypoglycemic coma. The basal metabolic rate was low. Epinephrine brought her out of coma, and she was kept free from attacks, with a normal blood sugar by the administration of suprarenal and thyroid extracts.

Pettersson, as cited by Wauchope, (162) reported a similar case in a woman who had defective skin and nails, absence of axillary and pubic hair, amenorrhea, low basal metabolism, low blood pressure and low blood sugar. In a hypoglycemic attack it fell to 25 mg. per cent.

These three cases point to the involvement of more than one of the endocrine glands.
The physiology of the liver in relation to carbohydrate metabolism has already been discussed in the section on physiology, and has been mentioned in the section on pancreas, thyroid and adrenal gland.

Many cases have been reported in which destruction of the liver, and therefore of the glycogen reserves, was associated with hypoglycemia.

Underhill, (156), in performing experiments on dogs in an effort to find a treatment for diabetes by producing it experimentally, found that giving a dog hydrazine in doses of 50 mg. per kilogram that a distinct lowering in blood sugar was found. At necropsy fatty metamorphosis of the liver was found.

Wagner and Parnas, 1921, as cited by Howland, (77) reported a case of hypoglycemia which was considered to be associated with failure of the liver to fix dextrose as glycogen, because of a failure to obtain hyperglycemia on epinephrine injection.

Cammidge, (23), says that mild forms of hypoglycemia due to defects in the functional activity of the liver are not at all uncommon. He says this may arise from defective formation of its glycogenolytic ferment by the liver. Cases due to defective functional activity of the liver accentuated by a toxemia of hepatic and intestinal origin when treated for the toxemia had no recurrence of hypoglycemic symptoms. In 1930, Cammidge, (25) reported 200 cases with low blood sugars. There was a notable hereditary phase as 36 per cent occurred in blood relations. Low blood sugars were found in 70 per cent of the young. The hereditary phase was seen in greater part in early life, as the parents of 36 had
low blood sugars. A chronic intestinal infection was found in nearly all cases, and constipation was of long standing. The liver was affected by the intestinal toxemia. He states that the fundamental defect is in the liver. He says that hypoglycemia due to hepatic defect is common in children as well as adults. This may be hereditary or due to some infection.

Carcinoma of the liver has been found to result in symptoms of hypoglycemia. Three cases are reported.

The first by, Nadler, (119) in 1929. This patient was admitted to the hospital in coma; orange juice revived him. A nodular mass was found in the epigastrium. The blood sugar was 40 mg. per cent. At operation an adeno-carcinoma of the liver was found. Four months later he became worse, becoming delerious, and unable to eat. He went into one hypoglycemic after another, always revived by slucose intravenously. He finally died in profound hypoglycemia; blood sugar was 13 mg. per cent. At autopsy a primary liver sell carcinoma was found. The tumor contained no insulin and occupied three fourths of the liver. Deficient glycogen storage was present. The hypoglycemia was caused by a disturbance of the sugar mobilizing function of the liver. The functional activity of the remaining liver cells was impaired. The lack of response to adrenalin injection showed lack of storage of carbohydrate.

Crawford, (38) reported a primary medullary carcinoma of the liver in a patient that had hypoglycemia. The patient went into coma several times. Complete loss of ability to stabilize carbohydrate metabolism
was given as the cause of the low blood sugar.

The third case was reported by Beers and Morton, (11) in 1935. This case was essentially the same as that of Nadler and Crawford. A primary carcinoma of the liver was found occupying 75 per cent of the liver. The tumor contained no insulin. The blood sugar of this patient was 18 mg. percent at the time of death.

Josephs, (87) stated that there was a fairly constant relationship between disease of the liver and hypoglycemia. Phosphorous, chloroform, and hydrazine poisonings give extensive liver damage and result in low blood sugar as result of the lack of storage of glycogen and loss of the liver's function in carbohydrate metabolism. In acute yellow atrophy of the liver, hypoglycemia has been demonstrated for the same reasons. Fatty infiltration is most commonly found. Josephs further states that in recurrent vomiting of children there is a hypoglycemia. This is due to alterations in the liver accompanying the severe and fatal form of recurrent vomiting. He presents cases of phosphorous poisoning which developed hypoglycemia.

Judd, Kepler, and Rynearson, (91) reported two cases of spontaneous hypoglycemia; one was a diabetic. Evidence that the cases were of hepatogenous origin is: The first case had a fatty metamorphosis of the liver. This was obvious grossly at operation. The patient had a prolonged phase of insulin resistance prior to onset of hypoglycemic symptoms which tends to incriminate the liver according to the authors. The hypoglycemic symptoms occurred at comparatively high levels; in de-
pancreatized hepatectomized animals, hypoglycemic symptoms appear at higher levels than in hepatectomized animals. The presence of diabetes in this patient argues for deficient production rather than overproduction of insulin. The second case wasn't so definite. It had only the microscopic findings of fatty infiltration.

LeCount and Singer, (94) reported a blood sugar of 67 mg. per cent in a patient who had symptoms of hypoglycemia. There was fatty infiltration in the liver. This patient had been a drinker of alcoholics.

Pribram, (131) in 1928, says that if the glycogenetic power of the liver and muscles is poor there will be a corresponding decrease in dextrose production with subsequent glycopenia. Cirrhosis of the liver was produced in dogs and it was found that some of these died suddenly due to disappearance of glycogen from the liver.

Shanks and Allen, (140) presented a case of hypoglycemia due to functional interference with the storage or release of glycogen in the liver and muscles. The patient was a very active athlete and had then taken up a very sedentary life of an attorney, and took very little exercise. The causes given were, 1. atrophy of disuse of striate muscular system lessening the storage of quickly available carbohydrate in the muscles and liver, 2. constant emotional stress causing exhaustive syndrome with hypofunction of the adrenals.

John, (83) reported a case of hypoglycemia and death occurring in an old diabetic which had been dismissed from the hospital without insulin. One year later the patient was readmitted in coma. The blood
sugar was 30 mg. per cent. At autopsy atrophic cirrhosis of the liver was found, carcinoma of the liver, and hypertrophy of the islands of Langerhans. The cause of the hypoglycemia was placed on the hypertrophied islands, but the liver condition was considered.

A case of parenchymatous hepatic degeneration was presented by Moore, O'Farrell, and Headon, (117). The patient suffered hypoglycemic attacks; at times the blood sugar went to 25 mg. per cent. Intravenous glucose gave symptomatic relief. The patient went into coma and died. Autopsy showed the subacute hepatitis. No changes were found in the pancreas. The authors believe that the cause was the disease of the liver interfering with its glycogenic function.

In discussing chronic hypoglycemia of childhood, Kramer, Grayzel, and Solomon, (92) site the German literature, namely, E. von Gierke who in 1931 describes a new clinical entity designated as, "von Gierke's Disease", or hepatonephromegalia glykopenica. The main characteristic findings are chronic hypoglycemia and hepatic enlargement due to excessive accumulation and fixation of glycogen.

The author presents a case of hepatic hypoglycemia where glycogen is not produced and is apparently replaced by fatty infiltration. He states that in all hepatic hypoglycemia the cause is either due to inadequate glycogenesis or glycogenolysis or both. This is the first case of its kind reported in the literature. This case was age nine months. Two others, a sibling and another two weeks old died, too, in the same family. The author believes it may be familial. There was inadequate
or absence of glycogenesis and glycogenolysis. Post mortem showed the liver extensively infiltrated with fat. The cause being aglycogenesis. Liver function was good for protein. There was absence of glycogen in the liver. This case presented is one of chronic post absorptive hypoglycemia. They believe that the reason for the fatty infiltration, eg., the conversion of the glucose to fat was because the liver wouldn't convert it to glycogen.

Briggs and Oerting, (16) in 1936, presented a case of severe hypoglycemia in a male patient age 68, who complained of weakness and loss of weight of 30 pounds. He developed nausea and vomiting with pain in the epigastrium. In the hospital the patient went into coma. The blood sugar at this time was 30 mg. percent. Intravenous glucose resulted in regaining of consciousness. The patient again went into coma and died. Autopsy showed a marked atrophy of the liver; it weighed only 800 grams. The pancreas was normal. Carcinoma of the stomach was also found. They believed that the marked cachexia and inanition secondary to carcinoma of the stomach was sufficient to deplete the glycogen reserve of an already damaged liver. The atrophied liver had deficient glycogen storage and they believe it played the greatest factor in producing this case of hypoglycemia.

These cases then, I believe serve to prove that a functional or organic disorder of the liver, relieving it of its glycogenic functions, and storage facilities, will produce spontaneous hypoglycemia.
MISCELLANEOUS ETIOLOGY
AND
CONDITIONS IN WHICH HYPOGLYCEMIA OCCURS

There are many pathological conditions and physiological states in which hypoglycemia occurs. This section will be devoted to this subject. An attempt will be made to explain whether the hypoglycemia is cause or effect in each case as given by the various authors.

ACIDOSIS: Talbot, Shaw, and Moriarty, (148) placed children on a fast from six to ten days as a therapeutic measure for idiopathic epilepsy. Three cases were observed with ages from eight to thirteen. They had blood sugars of from 83 to 91 mg. per cent at the beginning of the fast. In three days one had a blood sugar of 38 mg. per cent. The other two, in six days had blood sugars of 48, and 47. All three had acetone breath. All three had symptoms of hypoglycemia. This was the first report of hypoglycemia in children. Giving carbohydrate cleared up all symptoms. They say that in fasting, anti-ketogenic material is used up quickly, with the production of ketones and combination of acids with the alkali reserve of the blood, the carbon dioxide combining power is reduced. They say the same condition results in prolonged vomiting, cyclic vomiting, and at onset of acute infections. When ketosis is found, an interference with the availability of sugar or the ability of the body to oxidize sugar must be assumed.

ALLERGY: According to Cammidge, (26) a low blood sugar is a common feature of allergic disease. He presents two cases of asthma in which low blood sugar was found. The first case had a blood sugar of 35 mg. per cent at the time of an asthmatic attack; the other patient had a fasting blood sugar of 77 mg. per cent. These cases, however, also
showed a rapid rise of the blood sugar on tolerance tests, this indicated according to Cammidge, a defective storage capacity of the liver. He further believes that the hypoglycemia in these cases was due to defective liver function on a hereditary or acquired basis.

**DEMENTIA PRAECOX:** Raphael, Theophile, and Parsons, (135) conducted studies on carefully controlled patients of the dementia praecox group. Of eleven patients studied, ten had a fasting blood sugar below what was considered normal. All but one showed an increased sugar tolerance and in three hours the blood sugar was back to the original hypoglycemic levels. These blood sugars were from 75 to 110 mg. per cent. Four cases of manic depressive psychoses were studied that were in the hypomaniac stage, all four showed definite hypoglycemia and flat tolerance curves. The seven cases studied in the depression phase showed hyperglycemia.

**LATE DIABETES:** Gammon and Tennery, (50) in 1931, state that a terminal hypoglycemia in diabetic patients treated without insulin and not responding to dextrose had been observed many times. Jonas, (85) reviewed some cases and gives one in which a diabetic patient died in hypoglycemic coma ten days after suspension of insulin therapy. Joslin, (89) also reported some of these cases.

**EPILEPSY:** Harris, (67) made a study of hyperinsulinism and epilepsy. He states that, "a number of cases reported by careful and capable clinicians, in which the diagnosis of epilepsy had been made, have been associated with hypoglycemia assumed to be due to hyperinsulinism and in
some of these cases convulsions were controlled by dieting. In other cases of periodic epileptiform convulsions associated with hypoglycemia adenomas of the pancreas were found at operation, and their surgical removal resulted in cures of patients who otherwise would have been doomed to live only a few months, or a few years, with the constant fear of epileptiform seizures hanging over them. In a recent study a number of cases which had been diagnosed as epilepsy were found associated with marked degrees of hypoglycemia. This observation suggests that hyperinsulinism may be one of the precipitating factors in the etiology of a distinctive type of grand mal and petit mal. In other words hypoglycemia in such cases can be the trigger that sets off the epileptiform explosion in a person who has the constitutional convulsive tendency. If the hypoglycemia due to hyperinsulinism is proved to be a factor in the periodic attacks of convulsions in some cases now classified as idiopathic epilepsy, with the application of our present knowledge of the dietary management of hyperinsulinism, it seems probable that this type of epilepsy, unless associated with a neoplasm of the pancreas may be controlled by a diet that will maintain the patient's blood sugar level at a point high enough to prevent the seizures. "..."The fact that epilepsy is rare among diabetic patients suggests that the hyperglycemia may be incompatible with attacks of petit and grand mal. " Harris, however, says that he doesn't believe that hyperinsulinism is the cause of epilepsy nor does he believe that it is the sole etiological factor in any case of epilepsy. He believes that in a patient with convulsive
tendency, the hypoglycemia may precipitate the convulsive seizures.

Ziskind, Hollombe and Bolton, (173) in 1936, made a similar study and found that in 200 consecutive epileptic patients subjected to a 36 hour fast, all failed to show symptoms of hypoglycemia. They found that hyperinsulinism patients manifest signs of hypoglycemia before convulsions and all occurred at a time remote from last meal. They suggest a 36 hour fast to differentiate the hypoglycemic symptoms from true epilepsy.

EXHAUSTION: The hypoglycemia that occurs in exhaustion is well shown by examination of marathon runners. Levine, Gordon, and Derick, (95) in 1924, noted the appearance of exhaustion that some athletes manifest following a run or crew race was strikingly similar to insulin shock. Some runners at the finish of the race showed muscular twitching, extremal palor, cold moist skin, nervous irritability, and even collapse and unconsciousness. At the finish those who had normal sugar showed no signs of shock. The winner of the marathon had a normal blood sugar. Two showed asthenia and pallor at 65mg. percent. Four were prostrated. It is suggested that the adequate ingestion of carbohydrates before and during any prolonged violent muscular effort would be of considerable benefit as preventing hypoglycemia and accompanying development of the symptoms of exhaustion. The following year further studies were made on marathon runners by Burges, Kohn, Levine, Matton, Scriver, and Whiting, (20), in 1925. From the observations made the previous year they set about finding at what stage in the race the symptoms of hypoglycemia were likely to occur. During the training period they found that between
the fourteenth and eighteenth mile these appeared. They then in addition to giving large amounts of carbohydrate before the race, the runners were supplied with glucose candies to be eaten from time to time while running also tea at stations. In contrast to the previous year, blood studies showed levels in all runners to be normal, and there was a general improvement in physical condition. They conclude that the symptoms of hypoglycemia, following prolonged effort may be prevented by adequate and timely ingestion of carbohydrate.

HEREDITY: Investigation of this field was done by Carmidge, (24) in 1927. He said that the disturbance in function of liver, ductless glands and nervous system, and kidney giving rise to chronic hypoglycemia, appears to be both congenital and acquired. His breeding experiments in mice show apparently low blood sugar is a recessive character transmitted in accordance with Mendel's theory of heredity. This has not been definitely demonstrated in humans, but the occurrence of the condition in several members of the same family suggest it, especially in childhood.

INFECTIONOUS DISEASE: Neff, (120) found that hypoglycemia developed in a case following diphtheria. He believed that it was the result of liver damage and degenerative changes which would affect its glycogenic function. Gammon and Tennery, (50) say that certain infectious diseases such as diphtheria, cholera, typhoid, late tuberculosis, and experimental trypanosomiasis, are accredited by some authors with producing hypoglycemia.
INTESTINAL TOXEMIA: Cammidge, (24) states that as a rule chronic hypoglycemia is acquired and the most common cause is intestinal toxemia, as found by evidence of functional disturbance of intestine, with toxic absorption and hepatic insufficiency, overeating, especially protein foods, defective mastication, lack of exercise, worry and nervous strain appear to predispose to the development of hypoglycemia. Brougher, (19) found that in 14 cases of irritable colon all had hypoglycemia as their chief complaint. The patients like cammidge found were of nervous exhausted type.

LACTATION: Gammon and Tannery, (50) site Stenstrom, who reported hypoglycemic seizures in a nursing mother. The attacks were eliminated by cutting down the high fat in the diet, and eliminated by weaning the child. After weaning the same diet no longer produced symptoms. No explanation is given.

MENSTRUATION: Tedstrom and Wilson, (150) investigated the relationship of functional dysmenorrhea and menstrual hypoglycemia. Thirty-eight cases were examined that had symptoms. Every case with a fasting blood sugar below 80 mg. per cent, had either menstrual pains of varying degree or complained of marked nervousness, irritability, weakness, hunger, or excessive desire for sweets two or three days preceding onset of flow. All but one were relieved by carbohydrate feedings or measures to elevate blood sugar. Extra carbohydrate feedings relieved the premenstrual tension, nervousness, excitability etc., and menstrual pain in about 80 per cent of cases on which it has been tried. Eight patients
were dramatically relieved by intravenous injection of 25 c.c. of 50 per cent glucose. Several patients were relieved by the carbohydrate feedings even though the blood sugar was normal.

**MUSCULAR DYSTROPHIES:** McCrudden and Sargent, (110-112) found in three cases of progressive muscular dystrophy hypoglycemia and cases followed by treatment, the blood sugar rose parallel with the increase in strength. They found that in progressive muscular dystrophy there is a rapid fall of blood sugar in the first twenty-four hours of starvation indicating low reserve supply in the liver.

Prompt rise in blood sugar followed epinephrine injection in progressive muscular dystrophy testifies to the adrenal rather than hepatic origin of the disease. They conclude that the facts indicate that the myesthenia of progressive muscular dystrophy is due to hypoglycemia; that the hypoglycemia and fatty infiltration are due to glycogenesis of the carbohydrate of the food being probably changed largely to fat instead of glycogen, and that this impaired glycogenesis is the result of adrenal or other endocrine disease.

**PREGNANCY:** Titus and Dodds, (154) investigated the lowered blood sugar values in vomiting of pregnancy. They found a greater number of cases showed blood sugar below normal—less than 80 mg. per cent. They found that eclamptic convulsions were usually preceded by a sudden drop in blood sugar to levels classed as "relative hypoglycemia". The drop may be to a normal level if it was fifty milligrams per cent higher a few moments before. The convulsions were produced by the suddenness of
this drop which took place within a few minutes.

In hyperemesis they found the blood sugar may go to 25 mg. per cent with only a nervousness or tremor, because the process is slow. They believe that the underlying cause of toxicoses of pregnancy is a disturbance of carbohydrate metabolism on the side of deficiency, resulting chiefly from fetal demands. The success in treatment of hyperemesis and eclampsia with intravenous glucose further supports their theory.

Cornell,(37), reported two cases of hypoglycemia in pregnancy developing in the latter half of pregnancy. He postulates the cause is increased insulin from the baby as it is not unusual to see these babies lose more weight than normal.

Plass and Woods, (129) found that in pregnant women near term, starvation for 12 hours leads to blood sugar reductions similar to those observed in non-pregnant individuals, but fasting for 50 hours, reduces the blood sugar to levels considerably below those recorded for non-pregnant. In 14 among 53 such patients the blood sugar fell to less than 40 mg. per cent, and in one case to 30 mg. per cent.

Development of a marked starvation hypoglycemia with acetonuria produces no signs or symptoms of toxemia of late pregnancy except that mild transient headaches are occasionally noted.

PREMATURITY: Van Creveld, (158) studied the carbohydrate metabolism of premature infants, and in a series of 60 cases he found lower blood sugar levels than normal ones at full term. He considers this due to the functional prematurity of the premature.
RENAL GLYCOEURIA: According to Wolf, (171) the parathyroid glands produce a hormone which maintains a normal calcium content of the blood, and through these activities exercises a strong controlling influence upon the permeability of membranes. Further he says permeability is diminished by calcium and increased by sodium ions.

Cammidge, (23) states that in renal glycosuria and resulting hypoglycemia, excessive permeability of the kidneys for dextrose are essentially dependent upon defects in the function of the parathyroids and that the term renal glycosuria gives a misleading impression of the true pathology of the condition. Occasionally cases of essential renal glycosuria occur that giving calcium has no affect. These are probably due to primary renal permeability for all chemical constituents of the blood and present in such normal percentages with no evidence of defective carbohydrate metabolism.

In 1927 he, (24) states that renal glycosuria gives rise to a simple form of chronic hypoglycemia. That may be a congenital defect, but more likely is due to a low blood calcium due to parathyroid insufficiency.

Jonas and Hoxie, (85) made similar observations.

SCLERODERMA: This disease according to Longcope, (97) affects the connective tissues of the entire body. There occurs deep pigmentation. Attacks of mental confusion and delerium occurred in his case repeatedly after short periods of fasting. These attacks were associated with hypoglycemia. Many symptoms of this case resemble that of Addison's disease. It is possible, according to Longcope, that disturbances in function of
the glands of internal secretion which occasionally accompany scleroderma, may in some instances occur as a result of involvement of these organs by the generalized connective tissue process, and thus do not have a direct bearing on the cause. In one fatal case showed atrophy of one suprarenal.

**ALIMENTATION:** Gammon and Tennery, (50) in 1931, have noted the secondary fall in blood sugar after ingestion of food has occasionally been sufficiently marked to produce slight symptoms of hypoglycemia.

Waters, (161) has noted three cases of hypoglycemia in persons who had previously had high carbohydrate diets. He believes the prolonged high carbohydrate diets stimulated excess insulin.

**TERMINAL:** Schmidt and Carey, (138) investigated the blood sugars of 33 patients a few hours before death and after death. In two cases they found it to be 129 and 140 mg. per cent 10 hours before death and at death 50 and 38 mg. per cent respectively. Four cases had blood sugars of 38, 31, 33, and 55 mg. per cent from one half to four hours before death. Thirty-six per cent of the cases studied showed terminal blood sugars of 28 to 75 mg. per cent. In many instances the hypoglycemia was suggested before death as well as at death. He postulates that there may be some relation of hypoglycemia to post operative shock.

Ashe and Mosenthal, (5) discussed a case in which the patient died in uremia with a blood sugar of 30 mg. per cent.

Terminal hypoglycemia in diabetes has already been discussed else-where.
VAGATONIA: Nielsen, (121) investigated the hypoglycemic reactions in patients suffering from vagotonia. He cites Eppinger and Hess in their monograph of 1915, where they said that increased carbohydrate tolerance was characteristic of vegetative nervous system imbalance which they called vagotonia. Nielsen says that vagotonia is frequent in patients who have reached middle life after years of strenuous work. In studying these, hypoglycemic reactions were found remarkably constant.

Vagotonia in addition to being in psychopathic states and in neurasthenics, is frequently the end result of strenuous life, fatigue of the nervous system and endocrines. Hypoglycemic reactions are frequently the incapacitating factor. Glycosuria occurs in about one half of the cases. In 1935 Nielsen, (122) stated that disturbance in the vegetative nervous system, since it plays great part in regulation of glands of internal secretion, it comes about that the disturbances in the sympathetic nervous system may have wide influence on these glands and produce a multitude of symptoms, such as chronic fatigue, fatigue on arising, periods of depression, no energy, blood shot eyes, hunger before meals, soreness about gall bladder, and feeling like being in a daze most of the time. He says that these patients are frequently called neurasthenic and nothing done about it.

Along this line, Hoxie and Lisherness, (78) made a study of 50 cases and found that the cause of the hypoglycemic symptoms in these patients didn't lie in the pancreas, rather it seemed to be a general depression of the metabolism of the body. They weren't clear whether the hypo-
glycemia is caused by the nervousness or vice versa. Since the hypoglycemia tends to disappear as soon as general nutrition of the patient improves, they believe that the hypoglycemia is a result of the general nervous state rather than the cause of it. They cite Falton as stating that there is a disorganization of the vegetative nervous system in disorders of carbohydrate metabolism, so the hypoglycemia may result from this rather than a lesion of the pancreas or hyperinsulinism. He also believes that the underlying cause is overwork, debilitating disease, worries, or some type of exhaustion, as when this condition of exhaustion is corrected, the blood sugar curves become normal.

**VITAMINE DEFICIENCY:** Harris, (66) states that a vitamin deficiency predisposes to hyperinsulinism. McCarrison, (108) said that foods low in vitamin predisposed to abdominal infections. Harris, (63) stated that the anatomic and circulatory relations of the pancreas would seem to make it particularly vulnerable to secondary involvement from gall bladder, intestinal, and other abdominal infections. Harris, (66) then concluded that if it is accepted as a fact that faulty diets predispose to the infections that play a part in the etiology of pancreatitis, the sugar saturated, vitamin-starved Americans, i.e., those who live largely on white flour bread, white potatoes, white rice, lean meats, sugar saturated coffee, and sugar laden desserts, with candy and soft drinks between meals, would seem to be prone to become victims of pancreatic disorders, including hyperinsulinism and diabetes.
The discussion of the symptoms of spontaneous hypoglycemia if taken up in relation to each of its many causes would be very complex, also there would be present the symptoms of the disease entity in which the hypoglycemic syndrome occurred. By necessity then, only those symptoms caused by hypoglycemia itself will be discussed.

Since the recognition of the clinical syndrome of spontaneous hypoglycemia, there have been scores of cases reported, each giving a description of the symptoms of their case. For this reason there has been a countless repetition of the symptom complex. I shall present the complex as summarized by various authors.

**INSULIN-REACTION SYMPTOM COMPLEX**

In 1922, Banting, Best, Collip, Macleod, and Noble, (7) in their experiments with purified alcoholic extracts of the pancreas, found that when injected into rabbits the blood sugar fell, and as the blood sugar fell, the rabbits exhibited highly characteristic symptoms, the earliest of which are signs of hunger and thirst, hyperexcitability and apparent fear. They found that the animal may recover from these earlier symptoms, but frequently, with active preparations, the hyperexcitability becomes extreme and clonic convulsive seizures involving the entire body and lasting for several minutes supervene. Between the convulsive seizures the animal is lying on its side in a more or less comatose condition with shallow, rapid and frequently periodic breathing. Most rabbits convulsed at a blood sugar of .045 per cent. Subcutaneous dextrose returned the animals to normal.
These experiments soon brought the use of insulin to the treatment of diabetes. Here again the symptoms of overdosage were found. Banting, Campbell, and Fletcher, (8) in their use of insulin in treating diabetics observed these reactions. They described this insulin reaction as follows:

"When the blood sugar percentage falls to .07 per cent under the influence of insulin, the patient becomes aware of it. He may first complain of hunger, or more often a sense of weakness or fatigue, and especially if it is his first reaction, he is conscious of some anxiety or of what he calls nervousness, or he may even show the signs of a definite neurosis with loss of emotional control, such as crying spells. Almost constantly present is a feeling of tremulousness. The patient may have some incoordination for fine movements. Vasomotor phenomena are common: pallor or flushing; a sense of heat or chilliness; almost always profuse sweat. The severity of these symptoms increases with the hypoglycemia, and the lowering of the blood sugar near to .05 per cent produces very acute distress or even mental disturbances, such as confusion and disorientation. A blood sugar near to .032 per cent resulted in a state of coma with hypotonia and loss of deep reflexes. One patient which asleep passed into a low muttering delirium as the blood sugar fell to .052 per cent. This was followed by uncontrollable hunger. One patient was quite irrational while his blood sugar was around .06 per cent. On another occasion he became deaf and had difficulty in articulation. Others have a vague feeling of uncertainty at a blood sugar of about .075 per cent."

This symptom complex was also noted by Fletcher and Campbell, (48)
Additional findings observed by them were that the level at which the symptoms appear is quite constant in a given patient, though not always so. They emphasize the profuse sweat and increased pulse rate. Vertigo and diplopia is mentioned. Marked excitement, emotional instability, sensory and motor aphasia, dysarthria, delerium, disorientation, and confusion, have all been seen. Syncope and collapse and rarely unconsciousness. Bradycardia has occurred. They found that some patients have symptoms at blood sugar between .08 and .09 per cent, while others experience no symptoms as low as .054 per cent. They observed that the symptoms were largely associated with the nervous symptoms.

It was these types of observations in patients that had never received insulin that Seale Harris, (64) found and subsequently called cases of hyperinsulinism.

**SPONTANEOUS HYPOGLYCEMIA SYMPTOM COMPLEX**

From analysis of reported cases the symptoms of spontaneous hypoglycemia resemble insulin shock, but the intervals are shorter and the seizures are more severe. The actual seizure may be described as follows: A sense of weakness and extreme fatigue assails the patient, usually after a short fast; if walking, he feels unable to proceed a step farther; a vague nervousness supervenes; the hands tremble; sweat breaks out on the body; an intense hunger proclaims the need for food. Disturbances in vision are frequent: diplopia, dimness and loss of acuity are most common. Vertigo and ataxia may follow, as may nausea, vomiting and epigastric pain. Often an appalling sense of imminent dissolution is
experienced. The patient may cry out or sing. Mental confusion bec­
comes apparent to the observer in incoherent speech, irritability and
irrational action. Unconsciousness quickly follows, consisting of som­
nolence or deep stupor, which at times may be momentarily interrupted
by questioning or by painful stimuli. The stupor may last for several
hours or even for days. More frequently, however, unconsciousness is
soon followed by convulsions. The spasms are of the clonic type, big­
inning in the face with grimacing movements and spreading to all the
extremities simultaneously. The convulsions commonly are neither pro­
longed nor severe. Breathing is said not to be stertorous, and cyan­
osis is absent; the latter observation depends solely on the duration
of the convulsion. Foaming at the mouth is frequent; loss of sphin­
cteric control is uncommon. Nystagmus, trismus and inability to swal­
low have been noted. The convulsion is usually over in a few minutes,
and even without food, the patient, dripping with sweat and saliva,
becomes conscious. Recovery is complete without memory of the accid­
ent, however, temporary hemiplegia and occasionally other minor neur­
ologic residua, which clear up after several days have been noted.
Faresthesias of the tongue and lips, following or preceding the attack,
have been described. While in most cases the symptoms develop in the
progression described, certain more fulminant attacks resemble comp­
letely epileptic seizures. In other instances the episodes may be ab­
orted by the administration of carbohydrate. Recurrence of attacks with
increasing frequency is characteristic of pancreatic hypoglycemia.
With increasing frequency there is a tendency for the attack to become more severe. (50), (167), (163), (162), and (65)(69)

Marriott, (104) observed that the tendency to hypoglycemia is especially common in infants and growing children. In infancy the symptoms are irritability, colic and continuous crying, while in the older children emotional excitement, undue sensitiveness, fatigueability and often periodic attacks of vomiting and convulsions occur. A more detailed enumeration of the symptoms found in hypoglycemia will now be given.

-Neurological Symptoms-

Carr, (30) states that the nervous symptoms form a predominate part of the clinical picture of hypoglycemia. That they are varied and numerous, although not all present in one case. Further, they depend on the hypoglycemia itself and aren't particularly modified whether the lowered blood sugar is caused by the administration of insulin, liver damage or pancreatic tumor; the severity of the symptoms is in direct relation to the severity of the hypoglycemia.

According to Best, (13) the typical signs of profound hypoglycemia are dependent on the loss of integrity of nerve cells in the higher centers of the brain, and that there are no physical signs of hypoglycemia in the spinal animal or in one anesthetized by a general anesthetic.

These neurologic symptoms have been described by various authors. Carr, (30) states that the moderate lowering of the blood sugar may produce symptoms suggestive of organic weakness, but the more advanced
lowering brings on the neurologic manifestations namely stupor, complete amnesia, coma, twitching, and convulsions which have been mistaken for idiopathic epilepsy. Hemiparesis is sometimes seen. Carr emphasizes the amnesia by siting a case of a patient who had an auto accident, paid the damage, and later had no recollection of it. He believes that a diagnosis of various functional and organic nervous diseases may be made if the condition of hypoglycemia is not considered.

Goodhart, (55) found the following neurological findings in a patient with spontaneous hypoglycemia: phlegmatic to sullenness, to and fro tremor of fingers, hyperactive deep reflexes, absent abdominal and cremasteric reflexes, positive Babinsky, sluggish pupils, convulsions, ankle clonus, flacid paralyses of one leg, and coma. His patient when given glucose was relieved of all these neurological symptoms.

Wauchope, (162) in his review says that the symptoms associated with hypoglycemia are protean and cites A. Oppenheimer, (1927) in the German literature as saying that each patient has an individual reaction. Nevertheless the symptoms constitute a definite picture, derived principally from disturbances of the nervous system. Following the analysis of J. Wilder, (cited by Wauchope) the neurological manifestations are analyzed according to the nerve group affected, as, "The vegetative nervous system gives rise to symptoms such as sweating or cold, flushes, pallor, dimness of vision, flickering before the eyes, increase of pulse rate, and blood pressure; sometimes an increased flow of saliva; occasionally strangury; rarely paresthesiae."
Nielson, (121) who found hypoglycemia in a disturbance in the vegetative nervous system called vagotonia describes the symptoms as bloating of the abdomen, salivation, extreme hunger, weakness, mental fatigue, small pupils, insomnia, slow pulse, excess perspiration and fibrillary twitchings. He says that this vagotonic phase may alternate with phases of sympathicotonia.

Shanks and Allen, (140) say that the hypoglycemia is the distorting factor in the autonomic nervous system which brings the defense mechanism into play, so the symptoms of sympathicotonia are seen, which is an effort on the part of the autonomic system to elevate the blood sugar.

Wauchope, (162) states that the central nervous system is widely affected, and that the symptoms may be produced by disturbance at various levels. The general symptoms are headache and fatigue. "The bulbo-pontine system gives rise to disorders of speech such as stammering, difficulty in forming words, and slow articulation; ocular disturbance such as double vision, nystagmus, inequality of pupils; rarely deafness. The cortico-spinal group comprises paralyses, Babinski's sign, aphasia, perseveration, apraxia, motor irritability, incoordination, trismus, twitchings and convulsions which may be tonic or clonic, localized or general, and may resemble an attack of epilepsy; occasionally disturbances of smell and taste or paresthesia of the tongue; rarely incontinence of urine or feces. To the strio-thalamic system belong tremor, choreiform movements, fibrillary twitchings, grimacing, gesticulation, torsion, loud speech, rigor of muscles, atonia and katatonia.
Psychic disturbances are frequent and may be slight, like anxiety, depression, negativism, irritability, querulousness, or bizarre, for instance excitability, desire to sing, shout or dance, manic behavior; or they may result in dullness and confusion of thought, inclination to loiter and dawdle, to give random answers, compulsions, impulsive actions, wandering, fugues, homicide, suicide, amnesia, drowsiness, stupor, and coma."

There are other symptoms that are not directly derived from the nervous system, though they may be ultimately of nervous origin.

-Gastro-intestinal-

Hunger is the most frequent. It has been demonstrated (162) that in sixteen normal persons, insulin stimulated the secretion of gastric juice; the total amount of secretion and concentration of pepsin and hydrochloric acid were increased as the blood sugar fell. Occasionally there is disinclination for food. Refusal may be a part of the neurological symptoms, namely, negativism.

Nausea and vomiting was found to be a common symptom by Josephs, (87) especially in children. He found that the vomiting was variable in type. It may occur with one attack of hypoglycemia and not with the next, or it may be of uncontrollable type. The experiments of La Barre and Destree as cited by MacPhail, (162) showed that hypoglycemia provokes gastric contractions due to vagal action when the blood sugar reaches about .075 per cent, the pancreatic juice being at the same time diminished, provides a possible explanation for the vomiting.
Quigley, Johnson, and Solomon, (132) regarded the hunger as coming from excessive gastric contractions. Wilder, (167) states that both vomiting and diarrhea are rare. Friaram, (131) notes chronic constipation occurring in many cases.

CARDIOVASCULAR SYMPTOMS

Cardiovascular symptoms such as tachycardia, palpitation, and extrasystoles are common and are probably due to sympathetic stimulation. (167)(162) Mosenthal et al, (118) found in observing a patient that the blood pressure raises in a hypoglycemic attack, especially elevation of the systolic pressure.

Attacks of angina pectoris in hypoglycemia have been observed. Sippe, (144) stated that if glucose is necessary to maintain normal contraction of the myocardium, a low blood sugar would be expected to give symptoms of the impoverishment. This has been proved. Sippe says that the precordial pain and feeling of exhaustion associated with hypoglycemia are akin to those of cardiac disease, in that they are both produced by effort and relieved by rest. The attack in hypoglycemia may come on sometime after exertion, whereas the distress of angina pectoris occurs during and causes a cessation of the effort. Breathlessness on exertion, which is a common symptom in any state of debility and in cardiac decompensation, occurs frequently in hypoglycemia according to Sippe, also many patients in acute hypoglycemic shock complain of palpitation or flutter over the precordial area.

The pain may be of anginal character and distribution, but more
often is a constant ache, referred to the precordial area. Modern,(116) also reported a case of cardiac pain due to insulin overdosage.

Electrocardiographic changes also occur in hypoglycemia. Smith,(145) made a study of this and found that the principal changes were a flattening or inversion of the T wave or depression of the R-T interval. These changes, according to Smith, represent diffuse parenchymatous myocardial damage, and that they are referable to defective glycogen metabolism and diminished production of lactic acid in the heart is the best explanation to explain these changes. The details of this investigation are given in full by Smith.

Sippe, (144) found flattening or inversion of the P waves, low voltage QRS complexes, depression of the ST interval, and flattening of the T waves. His explanation was like Smith, the undernutrition of the cardiac muscle due to deficient glucose in the blood.

Bradycardia was noted by Ormond, (125) in a patient having spontaneous hypoglycemia. The patient was a male age 27 that had sinking spells and felt faint. He had a pulse of 42, and blood pressure of 115 systolic and 70 diastolic. He improved, the pulse rate becoming normal under high carbohydrate diet with six feedings.

-Respiratory-

Early in the attacks the respiration is accelerated, but when consciousness is lost, it is almost always slow and shallow. Cyanosis, however, is usually absent. Terminal bronchopneumonia has complicated many of the fatal cases in which necropsy has been performed. Dyspnea
somtimes occurs, and occasionally bradypnea, otherwise the respiratory
symptoms are not important. (167)(50)(162)

-Temperature-

The temperature is usually subnormal and may fall considerably with
the onset of hypoglycemia. (162) Stenstrom as cited by Wilder, (167)
also states that the body temperature falls in attacks of hypoglycemia,
to 95.9 degrees being recorded.

-Cerebro-spinal fluid-

Wauchope, (162) again refers to the monograph of Sigwald, 1932,
and quotes him as saying that in profound hypoglycemia the sugar level
of the spinal fluid may be depressed. The normal being 50 to 70 mg. per
cent, and sites a case where it went to 20 mg. per cent with a blood
sugar of 40 mg. per cent. The significance of the finding is not mentioned.

-Leucocytosis-

Klein and Holzer, 1927, as cited by Wauchope (162) found that leu-
cocytosis was constant in hypoglycemia, but did not run parallel with
the severity of the hypoglycemia. The maximum was 35,000 white cells
with a relative lymphocytosis.

-Onset, course, and occurrence-

The onset of the disease is insidious. An initial attack of hypo-
glycemic crisis, with complete loss of consciousness may occur without
previous warning, but mild episodes usually precede the development of
the more serious trouble. The course as a rule is chronic. (167)
Among patients that died, the length of life from the time of appear-
ance of symptoms till death varied from six months in the case of
McClenahan and Norris, (109) to seven years according to cases of Smith
and Seibel, (146). Cases that have the disease in a mild form and have
learned that the attacks can be prevented by eating frequently, have
lived longer. McGovern's, (114) case of a man age 44, had periods of
unconsciousness, and also suffered from episodes of amnesia since 1920.
The attacks appear at irregular intervals. These may be very infreq-
uent in mild cases and in the severe ones necessitate hourly feedings,
and usually as the disease progresses the interval becomes shorter.
(163)(167) In cases of pancreatic tumor this progressive nature is
more marked and the attacks of symptoms may occur several times a day.
Nielson and Eggleston, (123) had a case, (no.3) that had from 125 to 150
attacks in one day. The average duration of an attack is about one half
hour. (163) Rarely are the single attacks fatal, but Gray and Feemster,
(61) reported in cases occurring in babies of diabetic mothers, that the
sudden death of the child may be due to the hypoglycemia.

Gammon, (50) tabulates the cases of 31 authors and all but three
show that the onset of symptoms is with fasting, before meals, follow-
ing exertion, or rising in morning, with diarrhea, or after vomiting.
This shows that the onset is in definite relation to the intake of food--
neearly always at a time remote from a last meal. All but one of these
cases gives a history of repeated attacks, and the majority showed that
the attacks increased in frequency as the disease advanced.
Relation Between Blood Sugar Level and Symptoms

Various individuals may react differently to a given sugar level just as they react differently to other stimuli. (163)

The following table will indicate the levels at which various symptoms develop and the observers.

<table>
<thead>
<tr>
<th>Blood Sugar</th>
<th>Symptoms</th>
<th>Observer</th>
</tr>
</thead>
<tbody>
<tr>
<td>70-80 mg. per cent</td>
<td>Hunger, uneasiness, pallor</td>
<td>(24)(69)</td>
</tr>
<tr>
<td>60-65</td>
<td>Onset of symptoms, lethargy</td>
<td>(30)(3)</td>
</tr>
<tr>
<td></td>
<td>Faint, anxious</td>
<td>(24)</td>
</tr>
<tr>
<td></td>
<td>Bizzare symptoms</td>
<td>(69)</td>
</tr>
<tr>
<td>56</td>
<td>Unresponsive</td>
<td>(30)</td>
</tr>
<tr>
<td>55-65</td>
<td>Prostration, sweating</td>
<td>(167)</td>
</tr>
<tr>
<td></td>
<td>Depression, tremor</td>
<td>(66)</td>
</tr>
<tr>
<td>52</td>
<td>Weakness, dimness of vision</td>
<td>(71)</td>
</tr>
<tr>
<td>50</td>
<td>Symptoms of hypoglycemia</td>
<td>(66)</td>
</tr>
<tr>
<td></td>
<td>Unconsciousness, narcolepsy, hysteria</td>
<td>(77)</td>
</tr>
<tr>
<td>40-50</td>
<td>Symptoms of hypoglycemia</td>
<td>(77)</td>
</tr>
<tr>
<td></td>
<td>Sensory and motor aphasia</td>
<td>(24)</td>
</tr>
<tr>
<td>48</td>
<td>Incoherent, staring, fixed expression, stupor, tremor</td>
<td>(172)(30)</td>
</tr>
<tr>
<td>45</td>
<td>Drowsy, hands clammy</td>
<td>(77)</td>
</tr>
<tr>
<td>44</td>
<td>Deep stupor</td>
<td>(30)</td>
</tr>
<tr>
<td>42</td>
<td>Involuntary muscle movements</td>
<td>(30)</td>
</tr>
<tr>
<td>32-42</td>
<td>Coma</td>
<td>(109)(71)</td>
</tr>
<tr>
<td>40</td>
<td>Coma</td>
<td>(77)</td>
</tr>
<tr>
<td>35</td>
<td>Generally unconscious</td>
<td>(24)</td>
</tr>
<tr>
<td>31</td>
<td>Blurred vision, diplopia</td>
<td>(163)</td>
</tr>
</tbody>
</table>
There is great variability in the level at which the various symptoms of hypoglycemia occur.

Maddock and Trimble, (103) found that patients on insulin therapy often had blood sugars of 50 mg. per cent for six hours and had no symptoms. Phillips, (128) in his discussion on island hypertrophy mentions seeing a case of a negro where the blood sugar was 54 mg. per cent and no symptoms. Neil, (163) had a case where the blood sugar was 37 mg. per cent, and also another case where the blood sugar was too low to read, the only symptoms present were nervousness and profuse sweating. It might be stated here that a single blood sugar determination does not rule out hypoglycemia because according to Nielson and Eggleston, (123) the blood sugar may be normal when no symptoms are manifest.

In discussing chronic hypoglycemia, Cammidge, (24) states that there is more variability of the symptoms and a much lower level may be found without symptoms because of the adaptability of the body. He has seen cases with 40 mg. per cent without symptoms. In simple wild cases a persistent weariness and development of unusual fatigue with comparatively mild exertion especially when food hasn't been taken, develops. This leads to between meal eating habits. Mental and nervous phenomena are common, and defective power to concentrate, inability to pick

<table>
<thead>
<tr>
<th>BLOOD SUGAR</th>
<th>SYMPTOMS</th>
<th>OBSERVER</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 mg. per cent</td>
<td>Coma</td>
<td>(114)</td>
</tr>
<tr>
<td>20-30</td>
<td>Coma and convulsions</td>
<td>(47)</td>
</tr>
<tr>
<td>27</td>
<td>Stupor, inability to speak and convulsions</td>
<td>(163)</td>
</tr>
</tbody>
</table>
up a last thread of thought, while morning headaches improved by food, are not uncommon.

Seale Harris (69) classified the types of hyperinsulinism by the symptoms and blood sugar levels as follows: (1) mild type, (65-75 mg per cent) with bizarre symptoms, pale around lips, anxiety neuroses, weakness, trembling, sweating, all of which subside quickly with the use of orange juice; (2) moderately severe type, (55-65) with exaggeration of the first, prostration, increased anxiety, profuse perspiration, mental lapses, spasms, unconsciousness, all relieved in a few minutes by soluble carbohydrate; (3) severe type, (55-down) with recurring attacks of unconsciousness and convulsions often resembling narcolepsy or grand mal of epilepsy, and major hysteric phenomena and psychoses.

Symptoms of 65 patients as analyzed by Tedstrom (149) as follows:

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stupor</td>
<td>7</td>
</tr>
<tr>
<td>Mania</td>
<td>7</td>
</tr>
<tr>
<td>Coma</td>
<td>39</td>
</tr>
<tr>
<td>Diagnosed as epilepsy</td>
<td>14</td>
</tr>
<tr>
<td>Weakness and prostration</td>
<td>37</td>
</tr>
<tr>
<td>Loss of memory</td>
<td>20</td>
</tr>
<tr>
<td>Fatigue or tiring</td>
<td>10</td>
</tr>
<tr>
<td>Vertigo</td>
<td>10</td>
</tr>
<tr>
<td>Muscle twitchings</td>
<td>8</td>
</tr>
<tr>
<td>Hunger (excess)</td>
<td>12</td>
</tr>
<tr>
<td>Convulsions</td>
<td>26</td>
</tr>
<tr>
<td>Dull and listless</td>
<td>10</td>
</tr>
<tr>
<td>Sweating</td>
<td>19</td>
</tr>
<tr>
<td>Fainting</td>
<td>8</td>
</tr>
<tr>
<td>Change of behaviour</td>
<td>19</td>
</tr>
<tr>
<td>Tremors</td>
<td>8</td>
</tr>
<tr>
<td>Speech: 1. slow</td>
<td>3</td>
</tr>
<tr>
<td>Headache</td>
<td>9</td>
</tr>
<tr>
<td>2. monotonous</td>
<td>1</td>
</tr>
<tr>
<td>Epigastric pain</td>
<td>8</td>
</tr>
<tr>
<td>3. unintelligible</td>
<td>8</td>
</tr>
<tr>
<td>Babinski positive</td>
<td>8</td>
</tr>
<tr>
<td>4. motor aphasia</td>
<td>5</td>
</tr>
<tr>
<td>Nausea</td>
<td>3</td>
</tr>
<tr>
<td>5. slurring</td>
<td>1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>7</td>
</tr>
<tr>
<td>Nervousness</td>
<td>15</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>9</td>
</tr>
<tr>
<td>Visual: 1. diplopia</td>
<td>5</td>
</tr>
<tr>
<td>Vague paresthesias</td>
<td>6</td>
</tr>
<tr>
<td>2. dimness</td>
<td>3</td>
</tr>
<tr>
<td>Loss of sphincter control</td>
<td>5</td>
</tr>
<tr>
<td>3. dilated pupil</td>
<td>2</td>
</tr>
<tr>
<td>Irrational</td>
<td>5</td>
</tr>
<tr>
<td>4. blurring</td>
<td>1</td>
</tr>
<tr>
<td>Foaming at mouth</td>
<td>4</td>
</tr>
<tr>
<td>5. unequal pupil</td>
<td>1</td>
</tr>
<tr>
<td>Emotional instability</td>
<td>5</td>
</tr>
<tr>
<td>Mental confusion</td>
<td>14</td>
</tr>
<tr>
<td>Fear of death</td>
<td>3</td>
</tr>
<tr>
<td>Restlessness</td>
<td>8</td>
</tr>
<tr>
<td>Pallor</td>
<td>4</td>
</tr>
</tbody>
</table>
This shows fairly well the distribution of the symptoms per patient and
the frequency of certain symptoms as observed by Tedstrom in analyzing
these sixty-five patients.

The differential diagnosis between diabetic coma and insulin shock
is well done by Wolf, (171) and Neff, (120) as follows:

**DIABETIC COMA**  

**INSULIN SHOCK**

| ONSET | |
| Gradual with premonitory signs- for days. History of inadmissible leak of insulin in diet and omission of insulin. Polyuria and loss of weight. | Abrupt onset. History of overdose for insulin, insufficient food, or exercise, or emotional upset after insulin administration, hunger starvation. |

| PRODROMATA | |
| Extreme thirst | - none |
| Nausea and vomiting | - rare |
| No desire for food | - craving for food |
| Abdominal pain quite frequent | - emptiness in stomach, no pain |
| General malaise and weakness | - sudden weakness, nervous symptoms |
| Headache | - anxiousness, fear, sweating |
| Muscles flacid, no tremors | - inward shakiness and tremors |
| Somnolence becoming more and more pronounced, lapsing into coma | - pupils dilated |

| COMATOSE STAGE | |
| Deep respiration with air hunger | - respiration shallow or normal |
| Lips cherry red, face flushed | - profuse sweating |
| Acetone odor to breath | - normal or slight decrease tension |
| Softening of eyeballs | - diplopia before coma |
| Blurred vision before coma | - blood sugar below 75 mg. per cent |
| Blood sugar high | - normal |
| Decrease in CO2 combining power | - absent |
| Sugar and acetone in urine | - subnormal |
| Temperature normal | - skin cool and moist |
| Skin warm | - rarely fatal |
| Often fatal | - responds immediately to glucose by mouth or vein |
| Responds to insulin etc, after several hours. | |
The theories of the mechanism of the neurological symptoms of hypoglycemia were taken up by Dameshek, Myerson, and Stephenson in 1935, (42) as follows:

1. Dextrose is essential in the normal utilization of oxygen by the brain. In hypoglycemia the up-take of oxygen by the brain is reduced materially. This together with the well known sensitivity of the brain to diminution in its oxygen supply, may account for phenomena of twitchings and convulsions; the end result of lack of oxygen being coma.

2. Epinephrine theory. Against epinephrine as the cause of the symptoms are: 1. There is a diminution in symptoms with the injection of epinephrine when attacks of hypoglycemia occur, 2. Lack of dilation of the pupil in the insulin reaction, 3. The striking difference between the type of effect produced by insulin and that of epinephrine on the chemical constituents of the blood.

3. Water balance disturbance. Symptoms due to hydration of the central nervous system due to anhydremia of blood in hypoglycemia. Against this theory is their experiment of making blood counts and finding no changes during an insulin reaction.

Rudy, (137) discussed the relation of the blood sugar to the symptoms of insulin reaction. He reasoned that since hyperinsulinism, and the insulin reaction are accompanied by hypoglycemia, the reaction is due to the lowered blood sugar. He explains the mechanism as follows: The blood sugar is its own regulator by the alternating stimulation of the insulin and epinephrine secretions. A rise in blood sugar elicits a
a secretion of insulin which promotes glycogenesis and oxidation of the carbohydrate and inhibits glycogenolysis in the liver, and thus lowers the blood sugar level. A fall in the blood sugar below a certain level is followed by a discharge of epinephrine which stimulates glycogenolysis in the liver and thus raises the blood sugar level and so it goes on unless interrupted by other factors.

The severity of reaction from too much insulin depends on the amount of epinephrine appearing in the blood as counter reaction. An experiment to prove this was done by injecting five units of insulin at one time, and thirty units at another time. The blood sugar didn't go below 40 mg. per cent in either case, but the reaction was greater in the second was greater because of the greater secretion of adrenalin according to Rudy. The exact levels of blood sugar in each aren't given nor how the experiment was controlled.

The pallor, rapid pulse, profuse sweating, dilatation of the pupil resemble the results obtained by the discharge of sympathetic impulses. Hypoglycemia causes sympathetic activity with adrenal secretion and mobilization of sugar from the liver.

In the second stage the hypoglycemia is accompanied by convulsive seizures, and discharge of sugar from the muscles. These convulsions do not occur in denervated muscle even when the blood sugar is dropped and convulsions occur in muscles with the nerves intact.

Rudy states further, that as soon as hypoglycemia develops from an overdose of insulin, the symptoms are the same as in all other causes of
hypoglycemia.

The low blood sugar activates the sympathetic nervous system and causes hypersecretion of adrenalin. The pallor, profuse sweat, increased pulse rate, elevation of blood pressure, vascular spasms and dilatations are brought about by this effect.

If the blood sugar continues to remain low because of overdose of insulin, its effect continues and additional symptoms develop, such as convulsions and other neurological symptoms as well as mental symptoms. It may end if not checked in unconsciousness or death.

This second augmentation of symptoms according to Rudy is the result of the effects of the hypoglycemia on the central nervous system. The brain cells suffer lack of nutrition, because of the low blood sugar. The neurological and mental symptoms which occur in the first stage of the insulin reaction, namely, in the stage of the hypersecretion of epinephrine, are due to the effects of epinephrine on the vascular system. If no organic damage occurs, the recovery is rapid and complete. The longer the low blood sugar lasts, the more injurious is the direct effect on the central nervous system. This stage of hypoglycemia is serious because the cells of the central nervous system are delicate, and the damage to the cells may be lasting and at times even irreparable. Epinephrine also suppresses carbohydrate oxidation.

The anginal symptoms are also explained by Rudy as being, possibly, as adrenalin angina. It has been found that subcutaneous injection of adrenalin has precipitated anginal attacks. The pain arises as result
of anoxemia of a restricted part of the myocardium. Epinephrine increases the work of the heart because of the elevation of the blood pressure and the increase in metabolism. It increases coronary blood flow. If due to coronary disease the blood sugar and oxygen in blood flow in certain parts of the muscle is below normal, the increased oxygen requirement for the myocardium may not be compensated for completely by the increase in coronary blood flow. This disproportion between demands of the heart and the available supply of oxygen causes the angina. Epinephrine is a general vasoconstrictor and it is possible that there is constriction here, too. Insulin angina is apparently hypoglycemic angina which, in turn, is probably a combination of hypoglycemia and epinephrine effect on the heart. Glucose brings the E. K. G. back to normal.

Rudy states that in Addison's disease, the patients don't develop the first stage due to epinephrine, but immerse directly into the stage of central nervous system hyperirritability with convulsive seizures and unconsciousness, because there is no compensatory epinephrine reaction. He says that glucose may not bring back immediate relief because of the slow recovery of the central nervous system cells. Glucose must be continued a long time, since the reaction in the central nervous system may continue even with normal blood sugar. Further he states that patients with vagotonia aren't sensitive to adrenalin and so may have a low blood sugar before symptoms develop.

W. B. Cannon, (28) states that the explanation for the convulsions of hypoglycemia is that they are a part of an automatic diffuse mechanism
which comes into play when hypoglycemia occurs so that the blood sugar level may be raised by releasing the glycogen stored in the muscles after the sympathico-adrenal system as exhausted the glycogen stored in the liver. When the blood sugar falls it is met by an increased activity of the suprarenals and an overdose of adrenalin is thrown into the bloodstream. It is this hypersuprarenalism that he attributes the tachycardia, sweating, and some of the nervous symptoms. The symptoms of overdosage of adrenalin are similar to an overdose of insulin, according to Cannon. Because of this automatic regulation of blood sugar, most of the convulsions due to hypoglycemia recover spontaneously.

Powell, (130) states that the symptoms varying from drowsiness to narcolepsy, from mental deficiency to mental degeneration may be due to cerebral mal-nutrition, resulting from hyperinsulinism causing a low blood sugar. He advised blood sugar studies ("food supply to the brain") be made on all nervous mental cases.

Only fair agreement is seen as to the actual cause or mechanism of the symptoms. The adrenalin theory is contested, but there is agreement that the nutrition of the central nervous system is impoverished by a low blood sugar. Further investigation in this field will surely yield a more concise conclusion. Certainly from the material at hand no decisive conclusion can be made. Only an impression is gained.
The treatment of spontaneous hypoglycemia may be divided into eight groups, namely, prophylaxis, emergency or immediate treatment, dietary, insulin, surgical, endocrine therapy, Roentgen ray, and drugs. As in all medical practice, treatment usually is an individual matter; in this entity it is also. Therefore only the principles and not details will be given.

Prophylaxis

Prevention of the attacks of hypoglycemia in mild cases is not difficult regardless of the etiology. It can usually be accomplished by giving small meals at frequent intervals. An orange drink during the night or early in the morning is often sufficient. The entire dietary regime is directed against the production of symptoms and will be discussed under this heading. Another important consideration is exercise. Exercise reduces the blood sugar and obviously must be curtailed; at least the patient should be warned to be on his guard when he does exercise and to protect himself as far as possible by eating something, preferably a starchy food before exerting himself. Skipping of meals and radical dietary changes are to be avoided. (168)(167)(162)(50) The severe cases are very difficult to manage by prophylactic measures. Wilder, (167) says that the prevention of attacks in the severe cases is not successful and is a very tedious process if night feedings are required. Patients suffering from this unusual disease made the observation that eating relieves their attacks and they carry candy in their pockets to be eaten when the symptoms appear and thus learn their own prophylactic
Winans (169), Waters (161), and Harris (66), observed that persons eating heavily of carbohydrate foods showed blood sugar levels three hours after, lower than their normal level. It may be said that perhaps abstainence from high carbohydrate diets would prevent the stimulation of the pancreatic islands and thus avoid the development of a functional hyperinsulinism.

Cammidge, 1930 (25), advises early prophylactic treatment of the descendents of hypoglycemic families.

**Immediate treatment of the attack**

The acute emergency of the hypoglycemic attack, no matter what the cause is, is met by the administration of glucose. Wilder, (168) says that the quickest results are obtained if a solution of glucose is given by vein, but that table sugar may be used in an emergency (167), however, it acts slower than glucose since it must be first digested. Cane sugar is ineffective in all ways except by mouth. When the patient is unconscious and the intravenous glucose is not available, the dry sugar should be placed between the teeth and the cheek where sufficient absorption will occur in most cases to restore consciousness. Wilder (167), and Harris (65), state that absorption is poor from the colon, and enemas containing glucose are therefore not very effective. As soon as the patient is restored enough to swallow he can be fed orange juice, which provides a readily assimilable sugar.

The dose of glucose necessary to raise a very low blood sugar to
a level above that at which symptoms occur is small, ten grams often suffices. (168) Weil (163), says that 20 to 25 grams of glucose by vein should be sufficient to bring a patient out of an attack, and that this relief is prompt, but is of short duration unless carbohydrate is given by mouth to prolong the effect. He states further, that large doses of around 100 grams intravenously may be followed after a brief interval by a rapid fall in blood sugar level and the return of symptoms. Adrenalin in dosage of from .25 to 1.0 mg. is exceedingly useful in the treatment of an attack, but that it must be followed at once with glucose. (167)(163) Weil (163), says that all cases of hypoglycemia of pancreatic origin, except the one of Wilder's, that had the carcinoma of the islands with metastases, adrenalin elevated the blood sugar level and gave relief of the symptoms of hypoglycemia. He states that this drug is not applicable in cases of hepatic origin. Elevation of blood sugar with adrenalin takes from ten to sixty minutes. On the average there is an elevation of 30 mg. per cent in 15 minutes, and a fall to the original level or lower in 50 to 60 minutes. It is believed by Gammon and Tennery (50), that epinephrine is most valuable of all the drugs in relieving the immediate attack; pituitrin and ephedrine much less effective.

Dietary treatment

During the first years of treatment of this disease entity the high carbohydrate diet was used. Harris (64), treated his patients by dietary means. He gave them three meals a day with instructions to take a glass of milk or fruit juice three hours after meals. Thus these patients
received food six times a day. Most of his cases were relieved of their symptoms. In more severe cases he gave food every three hours. Foci of infection were removed.

Fletcher and Campbell (48), found that patients having insulin reactions were relieved by eating most anything. Their hunger and symptoms would disappear; glucose was the most satisfactory.

Josephs (87), prescribed high carbohydrate diets with feedings between meals and at bedtime.

Nearly all the cases reported early were treated with the high carbohydrate diets and in most cases the patients were relieved of the symptoms. Carbohydrate was given at the time of day that the symptoms appeared, even in the middle of the night in some cases. Weil (163), states that many serious cases are controlled by high carbohydrate diets. The carbohydrate amounted up as high as 450 to 500 grams per day. He reports a case that despite an intake of 580 grams of carbohydrate per day with frequent feedings the blood sugar level became lower rather than higher and mild symptoms persisted.

It is interesting to note that the dietary treatment of hypoglycemia has undergone changes similar to that in the treatment of diabetes mellitus. The changes are exactly opposite. The diets for diabetics at first being low carbohydrate then going to low carbohydrate high-fat diets, and then in recent years to a high carbohydrate diets. In hypoglycemia we see the opposite transition; first a high carbohydrate used then in more recent years the low carbohydrate high-fat diet.
This shift to the high-fat low-carbohydrate diet was probably instigated by the enlightening experiments of Sweeney (147), in 1927. Using medical students as subjects for the study, he showed that glucose tolerance tests are markedly affected by the character of the preceding diet. He studied four groups of cases in which the diet was arranged several days preceding the tests. One group was placed on a high-fat diet; a second group was given a high carbohydrate diet; a third group was given protein, and the fourth group was placed under starvation conditions. A fasting blood sugar was obtained. Then 100 grams of glucose were given. Blood sugar readings were made at one, two and three hour periods following the glucose feeding. The results were as follows:

In the group taking high-fat diet the blood sugar was higher at all periods than in other groups and was still much higher than normal at the end of the three hour period. In the cases under a high-carbohydrate regime, the blood sugar was much lower at the one and two hour periods and was practically normal at three hours. The glucose tests did not vary in the protein group. In the cases starved preceding the test, readings similar to those of the high fat group were obtained.

This experiment suggests that a high fat diet tends to decrease insulin production and that a high carbohydrate diet tends to increase insulin production. Sweeney concluded that the ingestion of carbohydrate activates a hormone which stimulates the formation of insulin. Under normal diet the activity of this hormone is well regulated. It seems that if a high carbohydrate diet is taken too long, there is an incre-
ased activity of the insulin producing hormone so that more insulin is generated than actually needed. With a high fat diet on the other hand, there is less activation to insulin production so that blood sugar regularly is at a higher level.

Acting on this theory, Waters (161), placed three patients suffering from the symptoms of hypoglycemia. Every one of these patients improved considerably. He also concludes that a diet reducing the carbohydrate intake and increasing the volume of fats seems to diminish an excessive insulin production and to raise the blood sugar level.

Shepardson (141), agrees that the obvious treatment for the hypoglycemia is the giving of carbohydrate in quantities sufficient to maintain the blood sugar at about 100 mg. per cent. As a rule most cases can be handled with six to eight feedings a day and restore the patient to normal. There are some cases that don't respond, however, he states, and presents a case in which the frequent carbohydrate feedings fail to relieve the symptoms. This author states that the administration of a high carbohydrate diet does not in any sense tend to relieve the cause of the condition, namely, an overactivity of the insular portion of the pancreas. He cites authors including Sweeney, that have shown that carbohydrate is the ideal stimulus for insulin secretion, and states that it is this basis for the increase in the carbohydrate in the diets of diabetics. He then states that it is now generally recognized that if car-

is long withheld, the insulin-secreting function of the pancreas falls in abeyance. Shepardson then used the high-fat low-carbohydrate diets in
treating cases of hypoglycemia and was met with gratifying results.
The fasting blood sugar on one patient rose from 63 mg. per cent to 101 mg. per cent in spite of even increased exercise. The symptoms disappeared and the patient gained in weight.

Quoting from Shepardson (141, p.190), "This type of therapy, namely a low carbohydrate, high-fat diet, has the advantage of affecting the fundamental cause of the glycopenic syndrome, whereas a high carbohydrate ingestion may temporarily relieve the symptoms, although actually stimulating the insular activity of the pancreas, a condition which it seems should be avoided if permanent results are to be obtained. There is some delay in the effect of the high fat diet in elevating the blood sugar. Consequently in acute conditions it is questionable whether such a regime would act sufficiently rapidly to be of clinical use. However, in the patient in whom the chronicity of the disturbance is well established and in whom a short delay will make little difference, there is apparently ample justification for this procedure. It furthermore has the merit of bringing about a feeling of well-being which is not surpassed and in some instances not equalled by that obtained with frequent high carbohydrate feedings, nor must the patients appetite approach the Gargantuan proportions so often necessary to eat six or eight times daily. Finally, the fats have a definitely inhibiting influence on the process responsible for the glycopenic syndrome."

The success of the high-fat low-carbohydrate diet was confirmed by Wilder (167), Harris (65), and Weil (163).
Harris (70), in 1936, in discussing the dietary treatment of hyperinsulinism, says that each patient has to be dieted to suit his particular needs. The diet should nourish the patient properly and provide sufficient carbohydrates, proteins and fat, and vitamins. The carbohydrate content should be lower than the diet for diabetics. He further confirms the observations of Shepardson and Weil, that the high carbohydrate diet stimulates the formation of insulin, further proving the fallacy of a diet high in soluble carbohydrates in insulogenic hypoglycemia. In his hands the moderate protein diet has given the best results in treating chronic hyperinsulinism. He used diets consisting largely of three, five and ten per cent vegetables and fruits combined with a high proportion of fats with frequent feedings. He reasoned that the giving of carbohydrate in the form of vegetables and fruits which must be digested before being absorbed and metabolized, would be released as dextrose in small amounts at a time, and so would not stimulate the secretion of insulin. Fats, particularly cream, were given with meals and between meals, with the idea that they are emptied slowly from the stomach. Therefore, the metabolism of the carbohydrates mixed with fats would be slow compared to the rapid emptying of the stomach and the accelerated metabolism after the ingestion of carbohydrate meals without fats. The diet prescribed by Harris for the average adult of average height and weight is of about 2250 calories derived from 90 to 150 grams of carbohydrate, 60 to 75 gm. of protein and the remainder from fat consisting largely of cream and butter. The food intake is divided into from five to seven feedings per
day. The obese patients are put on 1260 calories; 120 grams of carbohydrate, 60 grams of protein, and 60 grams of fat. Their activity is limited also. Feedings are six to eight a day. The underweight asthenic patients with hyperinsulinism are given 90 to 150 grams of carbohydrate, 60 to 75 grams of protein and 200 to 300 grams of fat. Harris says that the food should be weighed and measured just as accurately as the diets of diabetics, and careful blood sugar studies should be made on each patient for a few days after being placed on the diet. The patient should be impressed with the necessity of moderation in all things especially physical exercise, also should be taught all the rules of personal hygiene adapted to his particular needs, just as the diabetic patient is taught how to live and enjoy health even though he has the handicap of a crippled pancreas.

Treatment with insulin

The treatment of hyperinsulinism by the use of insulin was advocated by John (84), in 1934. Since the pancreas could be trained to increased production of endogenous insulin, he reasoned that it could be possible to train it to secrete less insulin. To understand the details of this method of treatment John is quoted. "A brief review of biochemical changes in the blood stream in hyperinsulinism may help to answer the question. In the morning the patients have a low blood sugar. Following a meal, the level of blood sugar rises and when it reaches a certain height, this postprandial hyperglycemia stimulates the pancreas to pour out insulin into the blood stream and the blood sugar begins to drop."
Normally the blood sugar reaches a certain level below 120 mg. per cent at which the insulin supply is automatically decreased or discontinued; in patients with hyperinsulinism, however, this regulation does not take place and the blood sugar continues to fall to a very low level when the symptoms of hypoglycemic shock appear. This process repeats itself after each meal.

Thus the upper level of the blood sugar curve represents the point at which the islands of the pancreas are stimulated to produce insulin, and the lower level is the point at which the insulin reaction ensues because of the superfluous insulin in the blood and the consequent hypoglycemia.

By giving insulin (ten units) to such a patient three times a day, one half hour after meals, I reasoned that the following might be accomplished: a half hour or less after a meal the blood sugar has not yet reached the upper level of stimulation of the islands and the injection of insulin should prevent its reaching this level. With the exogenous insulin in the blood stream, hyperglycemia fails to develop and there is no stimulation for the excessive output of endogenous insulin, which in the untreated patient causes the lower level of shock to be reached. If the dosage is properly adjusted (and the patient is not getting insulin from his pancreas), then the drop of his blood sugar should not reach the lower level at which the insulin reaction becomes manifest. In this manner, then, the patient's blood sugar is kept between upper and lower levels, the pancreas is placed at physiologic rest and hypoglycemia is eliminated.
On February 23, 1933 John first tried this treatment on a patient suffering from hyperinsulinism. A moderately high fat diet was used and ten units of insulin was given immediately after meals. The patient had no reactions and after she went home remained well. In three months all insulin was stopped and the patient continued to feel well, also the patient returned to a normal diet and was still well. John has no explanation for the successful treatment except that the theoretical reasoning given did train the pancreas to produce less insulin. Five other patients were treated likewise with good results.

Harris (70) in 1936, used insulin in two cases with apparently good clinical results, though blood sugar studies were not made to prove that the blood sugar levels were higher after the use of insulin.

Surgical treatment

The first and foremost question that must be answered is, when is surgery indicated in hyperinsulinism? A recent article by S. Harris (70), states emphatically that in no case of hyperinsulinism should surgery be resorted to until the patient has given a full trial to properly directed dietary management. This dietary management must have been on a scientific basis just as the cases of diabetes mellitus are managed. At least a few weeks of dieting on a weighed and measured diet, calculated and prescribed to suit the individual is necessary. If the symptoms of hyperinsulinism cannot be controlled by this, then surgery should be considered. Harris then sets up the following criteria for exploratory operation: 1. "In the acute fulminating cases which develop rapidly and in
which hypoglycemic attacks with convulsions and unconsciousness cannot be controlled by intravenous dextrose therapy, and in which death seems imminent, 2. In the severe chronic cases that cannot be controlled by properly directed dietary management in a few weeks. 3. In cases with severe neuro-psychiatric symptoms of long standing in which on account of economic or social or psychic handicaps the diet cannot be carried out properly, or long enough to permanently benefit the patient."

The contraindications for surgery of the pancreas as outlined by Harris are: primary disease, or hypofunction of the anterior pituitary, the thyroid, or the adrenals, resulting in relative, or actual hyperinsulinism, because such an operation could not remove the cause of the symptoms; acute yellow atrophy of the liver, massive carcinoma of the liver, or the hepatic lesions that follow acute poisoning from hepatotoxins.

There is no way at present to determine for sure the nature of the lesion present in the pancreas. If it were possible to diagnose an islet cell adenoma or carcinoma before operation, the dietary regime could be omitted and the curative results of surgery be administered. (70)

Regarding the differentiation between hyperinsulinism resulting from neoplasm or from functional hypoglycemia, Gammon and Tennery (50), say that when tumor is present, there is a tendency for the disease to be more rapid in its development, more severe in its manifestations, and more erratic in behavior, and more likely to cause death.

Weil (163) stated that there was no indication for operation, but
failure to respond to dietary regime is indication for exploratory. A high sugar tolerance curve with a late drop to a very low level suggests tumor. He believes that cure can be anticipated when an adenoma is found and removed, but cure by resection doesn't offer much hope. He also states that the age of the patient doesn't help much in the indications, but that carcinoma is expected in the older individual.

Harris (70), says that if at operation an adenoma of the body or tail is found, it should be removed if possible, but if there are metastases to the liver, and extensive involvement of the surrounding structures, the case is inoperable.

The results of operative treatment according to Judd et al (90), depend on the condition found at operation. Carcinoma with multiple metastases, nothing can be done, but if a localized tumor of islet tissue is found and removed, the patient will recover completely. Wilder (167), also states that the removal of adenomata will give cure. Many cases of adenoma of the islands of Langerhans have been removed, followed by complete recovery. A full account of these is given by Whipple and Frantz (165). Others, some of which I have already mentioned in the section on etiology are Carr et al (29), Womack (172), Tomkies (155) and Derick (43). Some were found at autopsy be McClenahan and Norris (109), and Smith and Seibel (146) and others.

Frequently exploratory operation fails to find the tumor that is the cause of the symptoms. It may be too small to be seen or imbeded and not found. (70) In Smith and Siebel's (146) case the tumor that was
found at autopsy was only one centimeter in diameter.

Although adenomata of the islands are usually single (70), it must not be forgotten that multiple ones are frequently present. For example the third case of Graham and Womack (57) was operated once and a small adenoma removed from the anterior surface of the pancreas, but the symptoms were not relieved. About a month later the second active adenoma was removed from the posterior surface of the tail of the pancreas and the symptoms were relieved.

Often the cases present typical clinical pictures of islet cell tumor, but none is found at operation. The Finneys (47), Holman (74), and Allen et al (3) have found this to be true.

A carcinoma when found early without metastases and removal has resulted in cure. Howland, Campbell et al (77) in 1929 were the first to get a clinical cure by resection of an early non-metastasizing carcinoma of the islands. Judd, Allen and Rynerason (90) also removed a carcinoma in a patient that remained symptom free for 22 months.

Pancreatic resections have been done in an effort to relieve hypoglycemia due to hyperinsulinism. The first one was in 1928 by Finney and Finney. (47) They removed about three fourths of the pancreas from a psychotic patient referred to them by Barker and Sprunt. There was definite improvement, but not complete relief.

The next case successfully treated by pancreatic resection was done by Holman, and Hailsback (74). This case was one due to a hyperplastic pancreas. They suggest that removal of the spleen and splenic vessels
would simplify the procedure and make mobilization of the tail of the pancreas easier and safer. Careful palpation for adenomata is emphasized.

Judd, Allan, and Rynearson (90), state that when there is no gross change in the pancreas, resection of a part of the gland may give partial or temporary relief, but the prognosis is uncertain. In their review of cases so treated, they find that the results haven't been encouraging, probably because not enough of the gland has been removed. Judd, Kepler, and Rynearson (91), agree with these statements and add further that nine tenths of the pancreas would have to be removed to get therapeutic results, because removal of this much is required to produce chronic diabetes in animals. They further state that it is difficult to exclude the presence of small islet tumors or diffuse hyperplasia of the islands at operation.

Allen, Boeck, and Judd (3), state that the failure of operations may be due to the insufficient removal of the pancreas. They find on examination of cases that only 30 per cent of the gland is removed, while at thyroidectomies fully 50 per cent of the gland is removed. They believe that more radical resection of the gland would give results comparable to results obtained in surgery of the thyroid gland. They conclude that the resection method is logical and through there have not been entirely satisfactory results, the more radical procedure should control the disorder.

In more recent years, then, the resection method has become more
successful. To further support this contention, Graham and Hartmann (58), in 1934 resected all but one eighth of the pancreas in a child one year old. The patient made a complete recovery and had no more symptoms of hypoglycemia. This is the youngest case operated on that I have found reported.

Similarly, a case operated by Berry (12), in 1935, 28 grams of the pancreas was removed and made a complete recovery. Thomanson (153), in 1935 also resected all but the head of the pancreas, and following the suggestion of Holman, already cited, he removed the spleen to facilitate the operation. This patient was much improved.

Harris (70), 1936, has had three cases treated by resections of from one half to five sixths of islet bearing tissue of the pancreas, all resulting in clinical cures. Two cases gave slight improvement, and one case where five-sixths of the pancreas was removed failed to control the hypoglycemia. He concludes that surgery offers relief in cases that cannot be relieved by proper diet. Removal of adenomas or carcinomas, of the islands of Langerhans has resulted in cures, but resection of the pancreas relieved the symptoms in about fifty per cent of reported cases.

Another possible surgical attack was related by Wilder (168), 1936. A patient with spontaneous hypoglycemia was operated, and no tumor was found. A double strand of thick silk was carried around the body of the pancreas and ligated anteriorly to the division of the celiac axis and the splenic artery. The condition of this patient was reported to Dr. Wilder by Dr. Major about three months later as being a mild diabetic.
The patient was completely relieved of the hypoglycemic symptoms. Regarding this Wilder says, (p.160) "While I dislike the idea of curing one disease by producing another, in this case it probably was justifiable. We are able to effectively to control diabetes, but are unable to manage severe cases of paroxysmal hypoglycemia."

Details of technique have been purposely omitted from the discussion of the surgical treatment as I considered it beyond the scope of this paper. If this is desired the following references have discussions of technique: (29)(3)(74)(77)(47)(165)(166) and (172).

**Endocrine therapy**

The use of the internal secretion of the pancreas in the treatment of hypoglycemia has already been discussed.

The use of endocrine replacement therapy largely resolves itself into the treatment of the various endocrine gland dysfunctions. The details of treatment of these dysfunctions is obviously beyond the scope of this paper. The literature is quite lacking on the use of endocrine therapy for hypoglycemia. For treatment of the endocrinopathies I refer the reader to Wolf's, "Endocrinology in Modern Practice", (171).

The use of adrenalin in the therapy has also been discussed; its use mainly in the immediate or emergency treatment of the attack.

Nielson and Eggleston (123) credited the whole gland product of the suprarenals with a part of their successful treatment of three cases of epileptiform convulsions due to dysinsulinism. Adrenalin has no effect when given orally, and it is questionable if any of the preparations of
suprarenal medulary substance are of value if given by mouth. (70)

The use of endocrine therapy was very successfully used by Goldzieher (54). The treatment of the hypopituitary groups of his cases responded beautifully; evidences of hypopituitarism disappeared and the blood sugars became normal and the symptoms disappeared.

Wilder (167), finds that although pituitrin has some antagonistic effect on the action of insulin, it has not proved of value in warding off attacks.

Weil (163) says the effect of pituitrin is similar to that of adrenalin, but less effective in its action.

Wolf (171) in discussion of hypopituitary syndromes advises replacement therapy with pituitary extracts; the whole anterior lobe extracts being the most effective.

Janney and Isaacson (81) used thyroid extracts in treatment of myxedema and other thyroid deficiencies and found that the blood sugar was elevated.

Campbell (27), found the giving of thyroid extract to a patient with post-operative myxedema, raised the blood sugar and symptoms of hypoglycemia disappeared.

Gardiner-Hill and Brett and Smith (51), found that giving thyroid extract brought the tolerance curves down to normal from a high sustained type.

Goldzieher (54), in 1936, gives more conclusive evidence in his cases of hypothyroidism that suffered from hypoglycemia. He gave thyroid ex-
tract orally from one fourth to four grains a day. The patients obtained
relief from symptoms in a remarkably short time.

Regarding renal glycosuria, Cammidge (24), advised giving para-
thyroid extract with some soluble calcium salts in cases where the blood
calcium is at fault in producing the glycosuria.

We find therefore that pituitary extract, thyroid extract, para-
thyroid extract, and suprarenal extracts have been used in the treatment
of hypoglycemia. The therapy is mainly directed against the glandular
deficiency disease itself.

Radiation therapy

Barrow (9), in 1933, was the first to use the Roentgen ray in the
treatment of hyperinsulinism. His patient had the typical symptoms of
hypoglycemia. This patient was given, on April 16, 1933, using 130
K. V. P., 4 ma., 3mm. Al. filter, 15 inch distance, 10 minutes to both
the anterior and posterior areas. From April 23, to 30th, the blood
sugar came up from 40 to 50 mg. per cent to 70 mg. per cent. May 3, the
same dose was given also daily from May 7 to 15th. Her fasting blood
sugar was 72 to 80 mg. per cent. May 16, June 22, and 23, one half
doses were given. Her fasting blood sugar was 90 to 100 mg. per cent
at that time. No. diet change was made throughout. He reports this
case as one temporarily improved, making no claim that radiation will
cure hyperinsulinism.

In 1935 Barrow (10) reported two more cases definitely helped by
x-ray. The first of these received 210 r. over both ports. The blood
sugar going from 45 mg. per cent up to 60 mg. per cent. The dose was repeated in seven days and it went up to 66 mg. per cent. In about 10 days 560 r. was given, and two weeks following this the blood sugar was 90 mg. per cent, and symptoms were greatly abated. The same dose of 560 r. was repeated two more times at weekly intervals and the blood sugar was found to be 100 to 120 mg. per cent.

The second patient was in a child age five, who had convulsive seizures of hypoglycemia. Six treatments were given over the pancreas using 90 K. V. P., 3mm Al, less than one fourth erythema dose given. The blood sugar came up to 100 and the child has had no further attacks and the child is normal in every way.

Harris (70), says that the possible dangerous secondary irradiation of the liver, stomach, duodenum and other organs, this therapeutic method should be used with great caution in attempting to decrease insulin secretion.

Sippe and Bostock (143), quote Terburggen and Heinlein as having produced a lethal hypoglycemia in rabbits by irradiation of the pancreas.

It seems, then, that the results of Roentgen ray therapy though not conclusive, gives encouraging results.

**Drug therapy**

The drugs that have been used, excepting the endocrine preparations, are not many. Tedstrom (149), found phenobarbital to be useful in one case in which the diagnosis was epilepsy and hyperinsulinism. A slight increase in the blood sugar was noted.
Harris (66) also found that bromides elevated the blood sugar in treatment of cases of epilepsy. Harris (70) states that sometimes drugs must be employed in cases of hypoglycemia particularly in those associated with epileptiform convulsions. He says that the bromides are not advised as the bromism may prove harmful. He recommends phenobarbital in one and one-half grain doses night and morning. The drugs are used as motor depressants and may help raise the blood sugar. He has used bel-laconna with the idea that it might inhibit the secretory activity of the islet cells. He has used it in mild cases of hyperinsulinism for several years seemingly with good results. Ephedrine is also recognized. He states that it mobilizes glycogen, and combined with diet and rest, may maintain the blood sugar level at a point high enough to prevent hypoglycemic symptoms.
(1). Spontaneous hypoglycemia or hyperinsulinism is a definite disease entity.

(2). Spontaneous hypoglycemia is a frequent and widespread disease entity, numerous cases having been reported by discriminating clinicians in many countries.

(3). It seems probable that the disease hyperinsulinism occurs almost as frequently as hypoinsulinism. Careful history taking, routine fasting blood sugars, glucose tolerance tests, and blood sugar studies at the time of unexplained nervous attacks, periods of unconsciousness, and convulsions, will prove many of them to be associated with insulogenic hypoglycemia.

(4). It has been proved definitely that lesions of the pancreas may cause hypersecretion of insulin, that hypofunction of the pituitary, thyroid, adrenal, and parathyroid glands, that liver disease, damage, or insufficiency, may give rise to upsets in the metabolism of carbohydrates and lead to the condition of a subnormal blood sugar level with the accompanying symptoms of spontaneous hypoglycemia.

(5). Hypoglycemia, therefore, is a condition of the blood giving rise to a definite symptom complex.

(6). The manifestations of the disease are protean, and identical to the symptoms reported from overdoses of insulin in the treatment of diabetes mellitus.

(7). Many theories and explanations are advanced for the mechanism of the symptoms of hypoglycemia. So far none have been conclusive.
Additional work is being done and will be done in an attempt to explain exactly what the changes are that take place in the body when the blood sugar is at a subnormal level.

(8). With the advancement of our knowledge of the physiology of the endocrine glands, pharmacology, food metabolism, surgical skill, and diagnostic methods, the patient afflicted with this entity has the right to expect relief from his symptoms, if not cure, unless his disease is beyond our present scientific therapeutic knowledge.
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