616.153.66–008.811.4

CRITICAL REVIEW[1]

HYPOGLYCAEMIA

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CONTENTS

History

During the ten years that have elapsed since Banting and Best isolated insulin in 1922, hypoglycaemia 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.

The fact that the blood-sugar may be reduced or absent has been known since 1849, when Claude Bernard, who pointed the way to almost every subsequent discovery about carbohydrate metabolism, demonstrated it in experimental animals. Before the isolation of insulin various experimental means had been found for producing the condition of low or absent blood-sugar. For instance, the glycogen stores of the liver were prevented from

[1] Received December 14, 1932.

reaching the general circulation by section of the nerve-supply of the liver (Claude Bernard (1849)); Kaufmann (1895)); by ligature of the aorta and vena cava above the diaphragm (Seegen (1890)); or by excision of the liver (Mann and Magath (1921)).

von Mehring (1889) and Minkowski (1892) produced hypoglycaemia by the administration of phloridzin, which lowers the renal threshold and allows overflow glycosuria; the blood-sugar is reduced and the glycogen of the liver depleted to make good the loss; the condition in experimental dogs is like that in human renal diabetes. Phosphorus poisoning was found by Frank and Isaac (1911) to lower the blood-sugar in rabbits by damaging the liver; a combination of phosphorus poisoning and phloridzin produced severe hypoglycaemia. Underhill (1911) found that hydrazine poisoning had a similar effect; 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 (Underhill (1916)).

Removal of the suprarenal glands in dogs reduced the blood-sugar, in the experiments of Bierry and Malloizel (1908), from levels averaging 0·13 per cent. before operation (five dogs) to levels averaging 0·088 per cent., within three and a quarter hours. Porges (1910) obtained considerably lower levels in dogs, which survived longer, for example, 0·033 per cent. nine hours and 0·032 per cent. thirteen hours after the operation.

Hypoglycaemia in man prior to the use of insulin. In man a low blood-sugar had been recognized before 1922 in three distinct conditions.

In 1910 Porges, who was the first to observe hypoglycaemia in man, reported three cases of Addison's disease in which the blood-sugar levels were 0·067, 0·052, and 0·033 per cent. respectively.

Cushing, in 1912, published a case of pituitary tumour, in which the fasting blood-sugar was 0·0394 per cent. Asthenia and pigmentation gave rise to the suggestion that the suprarenals also were involved, but the systolic blood-pressure was 140 mm. Hg.

Joslin, in 1921, published three cases in diabetic patients on the low diets of the Allen era where exhaustion of glycogen reserves was associated with hypoglycaemia. The blood-sugar in one of these cases fell to 0·04 per cent. (Case No. 19).

Thus the biological fact of hypoglycaemia was known to laboratory workers, and had been reported as a rare occurrence in clinical medicine; it was not, however, associated with a definite symptom complex until the results of over-doses of insulin were observed.

Insulin hypoglycaemia. In 1922 Banting and Best found that their extract of the pancreas invariably produced in rabbits hunger, thirst, hyper-excitability and fear, and finally convulsions. As soon as insulin was available for the treatment of diabetic patients similar symptoms were observed in man (Banting, Campbell, and Fletcher (1923)). They constitute a definite syndrome, and insulin hypoglycaemia became familiar both to physicians and to the patients themselves. In Toronto, in the early days, symptoms were

deliberately induced so that patients should recognize them and apply the remedy (Campbell and Macleod (1924)).

Spontaneous hypoglycaemia. The eyes of the profession being thus opened, it was soon perceived that the same symptom complex, associated with a low blood-sugar, occurred in non-diabetic patients and without the administration of insulin. Seale Harris, in October 1923, reported two such cases at a meeting of the Virginian State medical association and named the condition ' hyperinsulinism '. In January 1924 he saw a case in which hypoglycaemia occurred in a patient who, one year before, had had glycosuria. He considered this to indicate an unbalanced action of the islands of Langerhans, ' dysinsulinism '. He reported these three cases with two others in 1924, but in none was the pathological basis verified.

The next important landmark in the history of hypoglycaemia was set up in 1927 by Wilder, Allen, Power, and Robertson, who described an operation at the Mayo Clinic on a patient who had typical symptoms and even convulsions, and whose blood-sugar fell as low as 0·027 per cent.; a tumour of the pancreas was found, with a secondary tumour in the liver from which insulin was extracted (Case No. 2). Thus was established the proof that hypersecretion of insulin can cause hypoglycaemia.

In 1928 an operation was undertaken by Finny and Finny of Baltimore for the relief of similar symptoms; two-thirds of an apparently normal pancreas was removed, but with only slight improvement (Case No. 9).

In 1929 Howland, Campbell, Maltby, and Robinson reported a case in which a carcinoma of the pancreas was excised with complete clinical cure (Case No. 4).

Thus by 1929 spontaneous hypoglycaemia was a sufficiently definite disorder to justify surgical intervention. Unfortunately, in many of the cases the pathology is not clear, for clinical hypoglycaemia has been observed in a number of diverse conditions. It seems opportune now to review the harvest of a decade.

The Blood-sugar Level

Hypoglycaemia, hyperinsulinism (Harris), or glycoprivic intoxication (Fischler) has two aspects: first, the actual low level of sugar in the circulating blood, and, secondly, the associated symptoms.

The amount of sugar in the circulating blood varies under normal conditions both in man and in animals; the effect of insulin in lowering the blood-sugar also varies. The hypoglycaemic action in rabbits is used in the physiological assay of insulin, the convulsion level being estimated at 0·045 per cent., but it is necessary to take precautions to ensure uniform conditions and to calculate an average of many animals.

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. It is lower in children under three than in adults (Spence), and it is higher in old people owing to defective storage and a rise in the renal threshold to about 0·200 per cent. (Marshall).

Variations in the method used for analysis and the source of the blood make reported figures not strictly comparable; titration methods (e.g. Bang and Hagedorn) give lower values than colorimetic (e.g. Benedict and Folin). Joslin (1928) published a table showing the normal values according to seven different methods; the lowest (Bertrand) was 0·070 to 0·110 per cent. and the highest (Lewis-Benedict) 0·096 to 0·125 per cent. The plasma gives slightly higher values than whole blood (Joslin) and arterial higher than venous blood, except in diabetics, where the level becomes equal (Rosenow). Joslin, analysing whole blood, found that readings taken before breakfast in normal individuals were most frequently 0·100 per cent., varying from 0·080 to 0·110 per cent. Sigwald, who used the method of Bertrand and Baudouin on the plasma of venous blood, also considers the fasting level to be in the neighbourhood of 0·100 per cent., and the lower limit of the normal to be 0·095 per cent. The maximum normal level after food is under 0·180 per cent., the so-called renal threshold, above which sugar appears in the urine.

The point at which hypoglycaemia begins is even more difficult to determine than the normal level; it is, indeed, not a point but an elastic zone. Many cases have been reported in which symptoms of hypoglycaemia appeared between 0·090 and 0·080 per cent., e.g. by Weichmann. John reported reactions with even higher values. Sendrail and Planques cite eight authorities who agree that any reading below 0·090 per cent. constitutes hypoglycaemia.

Sometimes a rapid fall in blood-sugar, irrespective of the actual level, seems to bring on symptoms. Payne and Poulton reported a case in a diabetic woman of 46 in whom a fall from 0·320 to 0·280 per cent. regularly produced symptoms. Harrison, on the other hand, observed a fall from 0·328 to 0·053 per cent. in five hours without symptoms. Most observations, however, point to 0·080 to 0·070 per cent. as the usual level for the onset of clinical hypoglycaemia (Fletcher and Campbell; Campbell and Macleod (1925)). But in children the level is lower; Harrison estimated the blood-sugar in children under 12 years of age, in eleven of whom it was less than 0·050 per cent., without symptoms on twenty-eight occasions. The lowest value was 0·028 per cent.

Variation in severity of symptoms. As might be expected from these observations, there is no parallelism between the level of the blood-sugar and the severity of the symptoms. Usually the symptoms are slight or moderate above 0·065 per cent., but severe reactions are sometimes encountered; Labbé (1926) reported two such cases in which the blood-sugar was 0·060 and 0·074 per cent.

Similarly, at the other end of the scale convulsions and coma usually occur at levels below 0·045 per cent., but there are many exceptions. Klein and Holzer (1928), for instance, observed four insulin cases in which the blood-sugar was between 0·033 and 0·047 per cent. without symptoms, while Lax and Petenyi reported twenty-nine cases of hypoglycaemia following hyper-

glycaemia induced by an injection of adrenalin, in which the blood-sugar was under 0·070 per cent. with no symptoms of insulin intoxication; sixteen cases 0·060 to 0·070 per cent., seven cases 0·050 to 0·060 per cent., three cases 0·030 to 0·040 per cent., one case 0·028 per cent. Labbé (1931) reported similarly anomalous cases.

An explanation of these varying results is offered by Popper and Jahoda, who found that when caffeine was administered with large doses of insulin to healthy persons, no hypoglycaemic symptoms appeared, although the blood-sugar curves were the same as in other cases where insulin was given without caffeine and symptoms developed. They suggest that reduction in the blood-sugar alone does not cause symptoms, but that insulin intoxication is due to a component factor acting on the visceral nervous centres.

Even in the same patient the reaction may vary; Harrison instances a case in a baby of fourteen months. On one day there were definite signs with a blood-sugar of 0·044 per cent., and on another no reaction with a blood-sugar of 0·032 per cent. Laroche, Lebourdy, and Bussière report similar variability in an adult case of spontaneous hypoglycaemia; severe symptoms occurred on one occasion with the blood-sugar at 0·066 per cent., while on another day it was 0·058 per cent. with no symptoms.

Fatal hypoglycaemia. There is no fixed point from which recovery is impossible. Death has occurred at levels ranging from 0·065 to 0·015 per cent. (Sigwald); usually the readings are about 0·025 per cent. Labbé (1931) reported a case in a diabetic with cirrhosis of the liver in whom the blood-sugar fell to 0·014 per cent., with recovery from coma after lumbar puncture. Millard Smith recorded a glycaemia in a child of four who recovered.

The following generalization is approximately correct: the normal fasting blood-sugar is about 0·100 per cent.: symptoms of hypoglycaemia appear at about 0·080 per cent.; they become severe at 0·050 or 0·045 per cent., and death may occur with the level in the neighbourhood of 0·025 per cent.

Symptomatology of Hypoglycaemia

The symptoms associated with hypoglycaemia, sometimes called the glycopenic complex (Sigwald), are protean, and Oppenheimer (1927) says that each patient has an individual reaction; nevertheless they constitute a definite picture, derived principally from disturbances of the nervous system. Following J. Wilder, the neurological manifestations may be analysed according to the nerve-group affected.

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 paraesthesiae.

The central nervous system is widely affected, and symptoms may be produced by disturbance at various levels.

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, agraphia, perseveration, apraxia, motor irritability, inco-ordination, 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 paraesthesia of the tongue; rarely incontinence of urine or faeces. To the strio-thalamic system belong tremor, choreiform movements, fibrillary twitching, 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, maniacal behaviour; or they may result in dullness and confusion of the understanding and lead to disorientation, slowness of thought, inclination to loiter and dawdle, to give random answers, compulsions, impulsive actions, wandering, fugues, homicide, suicide, amnesia, drowsiness, stupor, coma.

There are in addition other symptoms detailed by Sigwald not directly derived from the nervous system, though they may be ultimately of nervous origin.

Of gastro-intestinal symptoms the most frequent is hunger. Roholm demonstrated in sixteen normal persons that insulin stimulated the secretion of gastric juice; the total amount of secretion and the concentration of pepsin and hydrochloric acid were increased as the blood-sugar fell, for example, from 0·097 to 0·029 per cent. The longing for food thus aroused indicates the remedy for the condition. Occasionally there is disinclination or even disgust for food. Refusal of sugar or chocolate is often merely a manifestation of negativism.

Vomiting is uncommon: Sigwald mentions it in spontaneous hypoglycaemia, especially in children where it may be associated with acidosis; the writer has seen it in a case of insulin hypoglycaemia. The experiments of La Barre and Destrée, who showed that hypoglycaemia provokes strong gastric contractions due to vagal action when the blood-sugar reaches about 0·075 per cent., the pancreatic juice being at the same time diminished, provide a possible explanation of the vomiting. Severe vomiting may, of course, produce hypoglycaemia by depriving the patient of food to meet insulin. Diarrhoea similarly may be a symptom or a cause.

Cardiovascular symptoms, such as tachycardia and extra-systoles, are common and are probably due to sympathetic stimulation. Angina pectoris is more serious and more difficult to account for. It is agreed that insulin is apt to precipitate an attack of angina in persons subject to it, for example, Case 31, and it may even bring on angina for the first time in persons with damaged myocardium, as happened in a case reported by Turner (No. 1)[2]:

[2] For convenience of reference abstracts of the cases quoted are numbered consecutively.

A woman of 58 had experienced slight dyspnoea and palpitation on exertion, her heart being enlarged, with calcification of the aortic arch. She had no cardiac pain until she had an attack of hypoglycaemia in which severe precordial and substernal pain radiated down the inner border of the left arm to the little finger; she had three such attacks and no further hypoglycaemia or angina.

Middleton and Oatway, in 1931, made a careful study of the cardiovascular reactions to insulin shock of eleven diabetic patients, and reviewed the experimental and clinical work so far reported; they noted the tendency for the development of arteriosclerosis in diabetes and emphasized the danger of depriving the heart-muscle of circulating glucose. The most important electrocardiographic change during hypoglycaemia is a decrease in the height of the *T*-wave; the *p*-wave is sometimes diminished and the amplitude of the *R*-wave decreased with increase of pulse-rate.

The blood-pressure usually rises at first and then falls; transitory aortic regurgitation has been observed (Weichmann and Koch (1928 and 1929)). The rise is probably due to the compensatory secretion of adrenalin (cf. the experimental work of Canon, *et al.*).

Respiratory symptoms are not important; dyspnoea sometimes occurs, and occasionally bradypnoea, as in a case published by Rathery and Sigwald where the respirations were five per minute.

Haemorrhages, for instance, haematuria (Lawrence and Hollins; Henderson), haematemesis, cerebral and meningeal haemorrhages (Ehrmann and Jacoby) have occurred during insulin treatment, but were not necessarily due to hypoglycaemia.

The temperature is usually subnormal and may fall considerably with the onset of hypoglycaemia.

Weichmann and Koch (1928) demonstrated that the ocular tension decreases as the blood-sugar falls.

The cerebrospinal fluid contains normally less glucose than the blood; the amount varies between 50 and 75 mg. per 100 c.c. (0·050 to 0·075 per cent.). Sigwald quotes authorities who cite figures as low as 0·040 per cent. and as high as 0·095 per cent. In diabetes and in hyperglycaemia produced by the injection of adrenalin, the glucose in the cerebrospinal fluid rises parallel with the sugar in the blood, but in hypoglycaemia it remains approximately stationary, so that the ratio of the glucose in the blood to the glucose in the cerebrospinal fluid, normally about 2 : 1, becomes less and may even be inverted (Sigwald). Nevertheless the glucose in the cerebrospinal fluid is sometimes lowered in profound hypoglycaemia, for instance, in Case No. 40 of spontaneous hypoglycaemia it was 0·020 per cent., the blood-sugar being 0·040 per cent.

Leucocytosis was found by Klein and Holzer (1927) to occur constantly, but not to run parallel with the severity of the hypoglycaemia. The maximum degree was 35,000 white cells with a relative lymphocytosis, and it was found to be higher in healthy persons than in diabetics.

The more common of these symptoms may be grouped together in stages

of increasing severity, and thus grouped they perhaps offer a more recognizable picture of the condition.

Slight hypoglycaemia, sometimes called the premonitory stage, is characterized by fatigue and lassitude, reluctance to make a physical or mental effort, and indefinite restlessness or malaise; children may become pale and tearful and neither adults nor children can describe their symptoms more exactly than as unpleasant. The blood-pressure is said to fall at this stage.

The second stage is attributable to a compensatory secretion of adrenalin; there is pallor or occasionally flushing, and a cold, clammy perspiration; palpitation of the heart; tremor of the hands; often a sensation of hunger or thirst; the temperature is lowered and the blood-pressure and pulse-rate raised. The most prominent subjective feeling in this stage is fear; the patient is afraid of his symptoms and the palpitation and tremor seem to him much more severe than they are found to be when tested. He also feels unnaturally nervous if he has to face any situation which requires courage; even a mild domestic crisis will unman him. A candidate for an examination had a slight attack and was amazed to find himself thrown into panic by the opening question; his hand shook so that his writing sprawled unsteadily across the page. He presently realized that a scanty lunch had brought about hypoglycaemia, ate a lump of sugar, resumed his usual firm handwriting, recovered his courage, and passed the examination. In children night terrors occur and fits of uncontrollable weeping which are cured instantly by a sweet and by nothing else.

In the third stage the senses become clouded, and the state of the patient often resembles that of alcohol intoxication; he becomes confused and dull, sees double, staggers, speaks thickly and indistinctly, often saying the wrong word, his eyes are glassy, and he is either perverse and sullen or unnaturally cheerful and hilarious. A doctor, in the early days of insulin treatment, was convicted of drunkenness, his plea of hypoglycaemia being disbelieved. He died a few months later of diabetes.

The subjective state is one of bravado; the patient may refuse to take sugar; he wants to see what will happen; it amuses him to see two objects instead of one and to watch one of them slip away to one side. He exhibits negativism in all its forms, and he resents the suggestion that he is suffering from hypoglycaemia. One patient insisted on driving his car home with one eye shut (to obviate the diplopia) rather than eat the chocolate he carried with him.

It is probably in this stage that impulsions, hallucinations, and fugues occur. Oppenheimer (1927) instances several cases. A man who began to undress a hundred yards from the station could not tell how he came there or what he was doing, and allowed himself to be taken home. Another patient mechanically poured milk over his head with a spoon and shortly after began to jactitate so violently that he almost threw himself out of bed. Children are often merely naughty and perverse; they may fly into a sudden rage, scream and kick, and refuse obstinately whatever is suggested.

One stage merges imperceptibly into another, but the fourth may be conveniently characterized as the one in which convulsions and paralyses occur; the degree of paralysis ranges from a transitory weakness, such as a drooping of one side of the mouth, to a profound hemiplegia; consciousness is dim, and the patient often lies in a passive state, apparently able to see and hear, but not appreciating what goes on around him. In children the drowsiness is apt to be mistaken for natural sleep. Convulsions may be preceded by twitchings and contortions, and may remain localized or become general epileptiform attacks with foaming at the mouth and even an epileptic cry.

Children, as in other circumstances, are more prone to develop convulsions than adults, but it is doubtful whether the association with hypoglycaemia is in many cases really one of cause and effect. Griffith, however, reported nine cases in which the blood-sugar was very low, even for children; in the case of a child aged sixteen months, the convulsions always ceased when dextrose was given; the blood-sugar on three occasions was 0·020, 0·028, and 0·036 per cent.

Coma, more or less profound, constitutes the next stage; often the patient can be partly roused; sometimes convulsions and twitching interrupt the flaccid condition; rarely hemiplegia or monoplegia can be detected.

The pupils are moderately dilated and react sluggishly, or not at all, to light. Babinski's sign is usually present and may be unilateral or bilateral.

Memory is lost when consciousness is lost; there is no remembrance of a convulsion, although events before and after may be dimly remembered; impulsions and fugues and actions, performed in somnambulist states, are completely forgotten.

In the last stage coma passes into death. Death from hypoglycaemia during insulin treatment for diabetes is rare in proportion to the number of patients who experience attacks. Sigwald collected twenty-four cases. Death in spontaneous hypoglycaemia is usually due to the underlying cause.

The stages outlined above correspond roughly to the degree of the fall in blood-sugar. The patient may pass quickly or gradually from one stage to another, or may plunge straight into convulsions or coma with little or no warning; this is particularly likely to happen where there is a state of unstable blood-sugar equilibrium.

The condition may be arrested, even without treatment, at any stage, and the patient gradually recover. With the administration of sugar and the return of the blood-sugar to normal all symptoms rapidly disappear; nothing is more dramatic in medicine than the swift recovery of the patient from convulsions, coma or hemiplegia, or from apparent intoxication to a completely normal state. It is comparable only to the relief of asthma by adrenalin.

No permanent harmful effects have been observed after attacks of hypoglycaemia; usually when the patient recovers he is perfectly well. In Case

No. 23 the patient, having been for ten hours in coma, felt energetic and fresh and came down early to breakfast.

Occasionally paralysis or other nervous phenomena last for several days, although hyperglycaemia is produced by treatment; Young observed a case in which hemiplegia persisted for two or three days. In Case No. 37 the patient experienced tingling and numbness of the hands and arms for five or six days after a severe attack; these are exceptions; recovery is usually immediate and always complete if the patient lives.

Pathogeny

It is probable that hypoglycaemia, or the tendency thereto, is inherited; Cammidge and Howard (1930) showed that in mice it is transmitted as a Mendelian recessive character, and Cammidge (1930) found a history of symptoms suggesting hypoglycaemia in the blood relations of 35 per cent. of a series of two hundred patients with spontaneous hypoglycaemia; in forty-eight cases he obtained proof by estimation of the blood-sugar that parents or near relations had also a low blood-sugar; in one instance a daughter, mother, and grandmother were affected.

Hyperglycaemia is a similarly hereditable character in mice, and Cammidge (1928) concluded from the pedigrees of diabetic patients that the defect of carbohydrate metabolism, giving rise to glycosuria, may be transmitted either as a recessive or as a dominant Mendelian character. It is, therefore, probable that further investigation into the families of the subjects of hypoglycaemia will show that it also is a Mendelian character.

Regulation of blood-sugar equilibrium. The fundamental cause of hypoglycaemia is believed to be an alteration in the balance of the internal secretions which regulate carbohydrate metabolism, and in the normal person keep the blood-sugar within certain limits. On the one hand, insulin, the internal secretion of the islands of Langerhans, lowers the blood-sugar, while adrenalin, the internal secretion of the suprarenal medulla, raises it. The secretions of the pituitary and of the thyroid glands play a part on the side of adrenalin, and it is possible that the internal secretions of the ovary and testis and of the parathyroids exert some action on the side of the pancreas. The interaction of these hormones is controlled from a nervous centre probably situated in the pons (Macleod). It is believed that an increased amount of sugar in the blood reaching the central nervous centre stimulates it to activate a secretion of insulin by way of the vagus (Sigwald; Macleod); and that, conversely, hypoglycaemia causes an increased secretion of adrenalin by way of the sympathetics (Burn). The low levels of the blood-sugar sometimes observed after glucose tolerance tests (Stenström (1927); John (1926)) are probably the result of undue stimulation of the insulin-producing mechanism by the sudden absorption of sugar into the blood-stream. It is possible that direct nervous stimulation of the liver to secrete sugar is an auxiliary mechanism set in motion by sudden calls to meet the demand of muscular

activity (Macleod). Himsworth has recently put forward the view that insulin is secreted continuously by the pancreas as an inactive substance, and that an activator which he calls 'insulin kinase' is produced in the liver.

The liver is the main reservoir from which sugar is liberated into the blood by the conversion of glycogen; exhaustion or lack of glycogen stores is therefore a factor in the production of hypoglycaemia. The glycogen stores in the muscles apparently play a subsidiary part (Campbell and Macleod (1925)).

The pancreas is the active member of this combination of agents, for insulin directly lowers the blood-sugar, but how it does so is not completely understood. It was formerly believed that the sugar removed from the blood by the action of insulin was deposited as glycogen in the liver and muscles, but this theory has been shown to be untenable in its simple form, for the increase of glycogen in the liver and muscles is not equal to the loss of sugar; probably an intermediate product is formed. Campbell and Macleod (1925) state generally that insulin creates a vacuum for sugar in the tissues, and more particularly that the tension of free glucose is reduced, so that sugar is removed from the blood; that this is not directly dependent on the polymerization of glucose into glycogen; that it is only partly due to increase in the combustion of carbohydrate. They suggest that the disappearance of sugar is perhaps associated with the reduction of inorganic phosphates which takes place at the same time, and that possibly an organic glucose phosphate is produced; Sigwald suggests additional possibilities viz., that sugar is transformed into fat or protein under the influence of insulin; that glucose α and β are transformed into glucose γ, or that glucose is transformed into lactic acid, which has been observed to increase in experimental animals during hypoglycaemia.

Thus the process by which glucose leaves the blood under the action of insulin is unknown, but it does leave the blood and ceases to be available to the organism. Clinically, conditions which increase the amount of insulin in the circulating blood are the most direct and potent causes of hypoglycaemia; they will be considered in detail later.

An injection of adrenalin directly raises the blood-sugar by a simple release and conversion into glucose of glycogen, particularly from the liver. In man the maximum glycaemia after an injection of adrenalin is reached in about one hour, and the fall to normal is succeeded by hypoglycaemia. When the glycogen stores are diminished or exhausted, adrenalin has no effect on the blood-sugar; it is not certain whether adrenalin also releases the muscle glycogen (Goldzieher (1929)).

Canon and his colleagues (1924), in an experimental study, concluded that the sympathetics and adrenals constitute a protective mechanism for mobilizing the sugar from the liver in hypoglycaemia, and that the convulsive stage of hypoglycaemia is due to the exhaustion of adrenalin or lack of glycogen stores.

There is considerable evidence, though no conclusive proof, that adrenalin is continuously secreted in health (Levy Simpson (1932)), but it is certain that disease or destruction of the suprarenals is often associated with hypoglycaemia. As has been stated, the first observation of hypoglycaemia in man was in cases of Addison's disease; but Addison's disease is due to destruction of the cortex of the suprarenals, whereas adrenalin is secreted by the medulla. Levy Simpson failed to produce any rise in the blood-sugar by injection of cortical extract in cases of Addison's disease, and considers that when it is associated with hypoglycaemia the secretion of the medulla is diminished or absent. Thus there is a lack of the counter-secretion to insulin.

The pituitary plays a complicated part in the regulation of the blood-sugar. On the one hand, pituitrin inhibits the action of insulin and produces rapid recovery if given in hypoglycaemia, and, therefore, tumours which diminish the secretion of pituitrin might be expected to further hypoglycaemia by allowing insulin unopposed action. The mode of action of pituitrin is not clear; it is agreed that it has no direct action on the blood-sugar; there is also evidence to show that it liberates glycogen from storage (Lawrence and Hewlett). But since, on the other hand, pituitrin also antagonizes the glycogenolytic action of adrenalin, it seems improbable that it acts by stimulating the sympathetics. Lawrence and Hewlett conclude that pituitrin has a balancing action on carbohydrate metabolism, and inhibits the action of drugs which tend to change the blood-sugar concentration away from the normal in either direction. It controls both the hypoglycaemia of insulin and the hyperglycaemia of adrenalin, but it effects no appreciable change in a normal blood-sugar concentration. Warren suggests that the influence of the pituitary on carbohydrate metabolism may best be considered as neurogenic.

The matter is further complicated by the association of hypoglycaemia with acromegaly, and J. Wilder put forward the theory that the anterior pituitary has an action on carbohydrate metabolism similar to that of the posterior lobe.

Whatever the mechanism, a certain number of cases of pituitary tumour are associated with hypoglycaemia, and others with glycosuria and hyperglycaemia (Colwell). Atkinson collected 1,319 cases of acromegaly from the literature, in 650 of which the presence or absence of glycosuria was mentioned; it was present in 32 per cent., and absent in 68 per cent.; a high sugar tolerance was observed in two cases.

The thyroid acts in the same direction as pituitrin and adrenalin, that is to say, hyperthyroidism is associated with hyperglycaemia. It is believed to act by making the liver more sensitive to stimulation, and more ready to discharge glycogen as glucose (Joslin (1928)); or by increasing the sensitivity of the central nervous system and thus enhancing the effect of adrenalin (Goldzieher). It follows that myxoedema is apt to be associated with a high carbohydrate tolerance and hypoglycaemia.

The parathyroids act, if at all, on the side of insulin. Extracts of

parathyroid have no effect on the blood-sugar level, but Winter and Smith found that in rabbits injected with a preliminary dose of parathyroid extract convulsions were induced by one-third to a quarter the usual convulsive dose of insulin.

The genital glands have not been proved to have any effect on the blood-sugar, though it has been suggested that their action is vagotonic, that is, on the side of the pancreas, and tends to promote hypoglycaemia. Pillman-Williams and Wills, in the study of blood-sugar curves during pregnancy, found that in many cases the curves became lower as pregnancy advanced. Herold considers that the vagus and the associated glands become more active in the later months of pregnancy and lead to hypoglycaemia. Lesions of the ovaries and testes have not been found in association with clinical hypoglycaemia, except in pluriglandular disturbances.

Conditions in which the glycogen stores are diminished are potential, and even actual, causes of hypoglycaemia ; they often intensify the action of insulin : for instance, diseases of the liver in which the reserves are destroyed, vigorous exercise which exhausts them, renal diabetes which eliminates an abnormal amount of glucose, and starvation which prevents replenishment, may produce or augment hypoglycaemia.

Theoretically, interference with the glucose-regulating centre in the pons might cause hypoglycaemia. Rathery, Dérot, and Sterne reported a case in which subarachnoid haemorrhage was associated with acute hypoglycaemia (Case 21).

It is obvious from the foregoing that there is no one cause of hypoglycaemia ; the conditions which produce it may be summarized as follows :

1. *Excess of insulin.* Therapeutic injections. Tumours and hyperplasia of the pancreas. Functional hyperinsulinism (idiopathic hypoglycaemia).
2. *Lack of opposing secretions.* Disease of the suprarenal glands. Pituitary tumours : posterior lobe, anterior lobe (acromegaly). Myxoedema.
3. *Lack of glycogen.* Destruction of reservoirs : disease of the liver ; wasting of muscles. Abnormal excretion of sugar : renal diabetes ; lactation. Active depletion of stores : muscular exercise. Failure to replenish stores : starvation.
4. *Interference with regulating centre.* Nervous disease affecting the pons. Overaction of the vagus.

Morbid Anatomy

The morbid anatomy is that of the primary condition, but since the symptoms are principally derived from the nervous system, the observations of Wohlwill on two cases of death in hypoglycaemic coma are of interest. The patients were diabetics, one aged 62 and the other 29 ; the first, a woman, had a mammary abscess, and was given 100 units of

insulin each day for three days before admission to hospital in insulin coma; the second died of hypoglycaemia after recovery from diabetic coma. There were no macroscopic lesions in the brain; microscopically there was widespread Nissl's degeneration of the ganglionic cells and an amoebic appearance of the glial cells; in the first case there was also diffuse swelling of the axis cylinders.

Spontaneous hypoglycaemia has now been recognized in some hundreds of cases, and in a large number of conditions; the most important of these is pancreatic hyperinsulinism; Gammon and Tenery, in 1931, made an elaborate analysis of thirty reported cases and included one of their own; in twenty-two of these the origin was considered to be pancreatic. Harris, in 1932, reviewed the reports of about fifty cases from American literature, where the greatest number are to be found.

Organic disease of the pancreas. 1. Carcinoma. Three cases only have so far been reported. Wilder, Allan, and colleagues (1927); Thalhimer and Murphy (1928); Howland, Campbell, and colleagues (1929).

The case of Wilder may be taken as an example (No. 2): A medical man 40 years of age had renal colic in 1924 and glycosuria early in 1925. His blood-sugar was normal, but there were traces of sugar in some specimens of urine; in November 1925 he began to feel faint and weak before meals, especially when he exerted himself; on one occasion he became stuporous after operating; trembling and sweating were prominent symptoms and a curious paraesthesia of the tongue and lips. For more than a year he warded off these attacks by taking frequent meals, and his wife woke him to give him sugar during the night. He had several severe attacks of convulsions and unconsciousness, and on one occasion (March 1926) coma lasted for two hours, and intravenous dextrose had to be given. The attacks became more frequent and more severe, and in September the patient came under observation. Exhaustive investigations were made; on one occasion his blood-sugar fell to 0·027 per cent. four and a half hours after a mixed meal, when he was in a stuporous condition interrupted by convulsive jerks. Epinephrin and pituitrin had no effect in raising the blood-sugar. His blood-pressure was about 110/60 mm. Hg. At operation an inoperable tumour in the tail of the pancreas was found with metastatic nodules in the liver. He died a month later. Histologically both pancreatic and metastatic tumours contained cells resembling those of the islands of Langerhans, and the extract from a large tumour of the liver produced hypoglycaemia in rabbits and was of the strength of 40 units of insulin per 100 grm. of tissue.

The case of Thalhimer and Murphy (No. 3) occurred in a woman of 57 who had had symptoms for two and a half years and latterly epileptiform convulsions; these attacks had no relation to food; the blood-sugar was 0·0355 per cent. a few days before death, the cause being only revealed at autopsy.

The patient treated by Howland and Campbell (No. 4) was a woman of 52, who during six years had attacks of confusion, faintness, and apprehension; she appeared to be intoxicated, perspired freely, and occasionally had a convulsion. The course of the illness was erratic; coma was infrequent, but during one period of unconsciousness the blood-sugar was 0·040 per cent. The case was remarkable in that a small tumour was successfully

removed from the pancreas with complete relief to the hypoglycaemic symptoms; the tumour contained insulin and had the character of a slow-growing carcinoma of the islands of Langerhans.

2. Adenoma of the pancreas, associated with symptoms of hypoglycaemia, has been reported in six cases: McClenahan and Norris (1929) (No. 38); Cushing (1930); Carr, Parker, *et al.* (1931) (No. 5); Smith and Seibel (1931) (two cases); Womack, Gnagi, and Graham (1932) (No. 6). In four of the cases the symptoms were completely relieved and the patients restored to health by removal of the tumour; in the cases of McClenahan and Norris, and one of Smith and Seibel, the tumours were found at autopsy.

The case of Carr, Parker, and their colleagues is typical (No. 5):

A youth of 19, who was attending a military college, came under observation with a diagnosis of epilepsy on account of convulsions and periods of odd behaviour of which he remembered nothing. One morning he heard the bugle sound the reveille and remembered nothing more until he found himself in hospital being examined; meanwhile he had dressed clumsily and had gone to the mess where his inco-ordinated movements in eating had drawn attention to the fact that he was ill. He slept for thirty-six hours in the hospital and woke up feeling well. These attacks became frequent, especially in the late morning; he became hungry, anxious, and confused, and continued, awkwardly, whatever he was doing; one day he drove through crowded streets for three-quarters of an hour with no recollection of it; sometimes stupor, with slight cyanosis and muscular movements, lasted for hours. His blood-sugar was found to be 0·044 per cent. when he was in a semi-conscious state. For six months he tried to ward off the attacks by a diet rich in carbohydrates and by taking sugar when one was imminent, but was not really successful and became more and more tired, till at last, after a severe attack, he consented to operation. An adenoma was resected composed chiefly of β cells, and the patient made a complete recovery.

Womack's case (No. 6) showed a different but equally typical symptomatology. A farmer of 44 used to be confused while out at work before breakfast; he felt as if he had had too much alcohol; one day, about two months from the onset, he was carried into the house unconscious; two months after this his attacks came on before he got up in the morning and were characterized by twitching, confusion, and random speech. He found that taking food in the night prevented the early morning attack, and he always carried sweets about with him in the day. When he came under observation his fasting blood-sugar was 0·050 per cent. and his blood-pressure 128/74 mm. Hg. A small tumour was removed from the pancreas and a clinical cure was effected. The authors were in some doubt, on examining the tumour microscopically, whether it was strictly an adenoma or whether it was feebly malignant, for there was no definite capsule, and normal pancreatic elements were included.

Hypertrophy of the islands of Langerhans. Phillips reported a case of a negro who was found unconscious and whose blood-sugar before death was 0·025 per cent. There was also high blood-urea and at autopsy subacute glomerular nephritis; the pancreas looked normal, but the islands were hypertrophied with an increase in the size of the cells by more than 50 per cent. of the normal, and Phillips thought these findings would account for

the low blood-sugar by an increased production of insulin. Two cases in children born of diabetic mothers, where the islands of Langerhans of the infants were considerably hypertrophied, support his view (Dubreuil and Anderodias; Gray and Feemster). On the other hand, in this case, the renal lesion may have lowered the threshold for glucose and have contributed to the low blood-sugar.

The proof of hypertrophy of the islands of Langerhans with hypersecretion, analogous with hyperthyroidism, is not yet established.

In this connexion the experiments of de Takats *et al.* (1930) are interesting; they produced hyperinsulinism in dogs by trauma to the pancreas (dividing it with a cautery), and thought that hyperplasia and hypertrophy of the island tissue resulted. Allan (1920) found hypertrophic islands in partly pancreatectomized dogs. de Takats and Wilder (1929) divided the pancreas by cautery in a diabetic boy with the object of isolating the caudal end and promoting atrophy of the acinar tissue and hypertrophy of the islands in accordance with experimental results; after recovery from the operation the boy's carbohydrate tolerance was increased.

Functional hyperinsulinism. Acute and chronic idiopathic hypoglycaemia has now been observed in a large number of cases of no definite aetiology in which functional hyperinsulinism has been postulated. Harris (1932) examined the fasting blood-sugar in 1,497 non-diabetics and found sixty-seven cases in which the level was 0·079 per cent. or under, the lowest being 0·045 per cent.; most of these patients, especially those whose fasting level was below 0·069 per cent., had symptoms attributable to hypoglycaemia. The course may be acute or chronic; Moore and his colleagues recorded a case (No. 7) in which the onset was acute and recovery complete with no recurrence during fourteen months:

> The patient was a married woman of 27 who was admitted to hospital in a semi-conscious condition; the next morning she was completely unconscious, slightly cyanosed, with deep, stertorous breathing, and frothing at the mouth. Babinski's sign was positive in both sides, the limbs were rigid, and there was blepharospasm. The blood-pressure was 90/70 mm. Hg; the urine contained a trace of albumin, no sugar, diacetic acid, or casts; the blood-sugar was 0·035 per cent. and the blood-urea 0·060 per cent.; 10 grm. of glucose in 20 c.c. of water were injected into a vein and the patient immediately recovered consciousness; there was achlorhydria, and the stools contained a large quantity of undigested starch.
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> A year before her admission she had had attacks of dizziness and an inclination to faint before meals; she had had three intravenous injections of novarsenobillon two months before admission, although the Wassermann reaction was negative; three days before admission she had become unconscious for a few moments, and on the day before admission had been unable to recognize her husband.

The authors consider the possibility that the failure to absorb starch was an aetiological factor in this case; under treatment undigested starch disappeared from the stools, and a test meal taken three months later showed

the presence of hydrochloric acid. It is also possible that damage to the liver by novarsenobillon aggravated the condition, but there were slight symptoms before it was administered. There was no recurrence of symptoms, though the fasting blood-sugar remained low (0·062 to 0·078 per cent.), and a blood-sugar curve taken fourteen months after the attack did not rise above 0·082 per cent. The condition was probably 'acute on chronic' hypoglycaemia like that in the case of Laroche, Lebourdy, and Bussiére which was complicated by a polyneuritis, possibly, as the authors suggest, due to prolonged hypoglycaemia. The patient had acute exacerbations with visual disturbance and even unconsciousness, although the blood-sugar did not fall very low (0·058 to 0·066 per cent.).

Chronic mild hypoglycaemia is not rare. Cammidge (1930) analysed 200 cases in which the age of the patients varied from 1 year to over 70; 128 of these had symptoms which improved when the level of the blood-sugar was permanently raised. Chronic infection, especially of the gastro-intestinal tract, was the most frequent exciting cause. In about 50 per cent. a low renal threshold was present, and this, rather than excessive secretion of insulin, is probably the cause in most mild cases; in fifty-one patients the defect appeared to be in the liver, and was in most cases inherited. Recurrent headaches, neurasthenia, lack of energy, and convulsive attacks were other manifestations. Harris's (1924) first cases may be taken as examples of so-called hyperinsulinism, and were described under that title. The symptoms were mild, always came on before meals, and were relieved by taking sweet food. His first patient, a physician of 60 years of age, had been an excessive eater of sweets, and Harris thinks that eating large amounts of carbohydrate may induce hyperinsulinism by stimulating the pancreas unduly. The second patient had a lowered renal threshold, his fasting-sugar being 0·065 to 0·070 per cent., and there were traces of sugar in the urine during a tolerance test, when the blood-sugar level did not rise above 0·167 per cent. The third case (No. 8) Harris believed to be one of 'dysinsulinism':

> The subject was an obese woman who, in 1923, weighed 220 lb. and passed sugar in the urine. A year later her weight was reduced to 160 lb. by dieting, and she began to experience weakness and nervousness at about one o'clock at night relieved by eating. Her blood-sugar during a 'nervous rigor' was 0·047 per cent.

All three patients were relieved of their symptoms by a diet low in carbohydrate and rich in fat taken at frequent intervals.

Partial resection of the pancreas has now been undertaken in four cases with a view to diminishing the secretion of insulin, but hypoglycaemic symptoms were not permanently abolished, nor did the blood-sugar remain at normal level afterwards.

In the case of Finney and Finney (No. 9) the patient was a woman of 53 whose symptoms began four years before, with the menopause, and consisted in periods of confusion and strange behaviour, giddiness, and diplopia

coming on before meals; for eighteen months convulsions had occurred from time to time. The taking of food dissipated an attack but began to lose effect. The fasting blood-sugar was 0·052 per cent. and the sugar in the cerebrospinal fluid 0·034 per cent.; 10 units of insulin provoked a typical attack unless glucose was also injected. Adrenalin raised the blood-sugar to normal. The blood-pressure was 116/80 mm. Hg. Laparotomy was performed, and about two-thirds of the pancreas was removed (22·5 grm.); both macroscopically and on microscopic examination it appeared normal.

Allan operated on two patients: (No. 10) a man of 52 had typical attacks on exertion or if meals were infrequent; symptoms came on when the blood-sugar fell below 0·060 per cent.; the lowest observation was 0·040 per cent. Fourteen grammes of the pancreas were resected with distinct temporary improvement but subsequent relapse (Allan (1929)).

His second patient (No. 11), a man of 47, had periods of excitement in which he sometimes became maniacal, chiefly during the night. At first food relieved or prevented the attacks, which came on when his blood-sugar fell below 0·050 per cent., but he became unable to work. A portion of the pancreas weighing 8 grm. was resected and was histologically normal; the patient was no better (Allan, *et al.* 1930). Holman removed one-third of the gland with amelioration of symptoms but no increase in the blood-sugar (Allan, *et al.* 1930) (No. 11 A).

There are several comments to be made on these cases:

1. The pancreas was normal in each case and, as Finney suggests, the cause of the condition may have been other than hypersecretion of insulin.

2. An insufficient amount of pancreatic tissue may have been removed. Experimentally resection of 90 per cent. of the pancreas in dogs is required to produce glycosuria and hyperglycaemia (Allan (1920)).

3. Allan's first case (No. 10), in which the hypoglycaemia improved and then relapsed, indicates the possibility of compensatory hypertrophy of the remaining normal tissue.

Functional overactivity of the islands of Langerhans is difficult to demonstrate, and it must be admitted that conclusive evidence is so far lacking.

Disease of the suprarenals. Addison's disease is often associated with low blood-sugar, probably in the majority of cases. Levy Simpson found the blood-sugar almost constantly subnormal (below 0·075 per cent.) in every case of six; the lowest values were in the neighbourhood of 0·050 per cent. Rowntree, in nine cases, found a fasting blood-sugar below normal; the lowest level, 0·045 per cent., occurred in two cases. Porges (three cases), Wadi, and many others have reported the association of Addison's disease with hypoglycaemia, which was in most cases incidental. Some of the symptoms of Addison's disease are similar to those of hypoglycaemia: weakness, fatigue in the earlier stages; convulsions, stupor, and unconsciousness in the later.

Wadi's case (No. 12) may be taken as an example in which the lowered blood-sugar seemed to play a real part. A man of 24 became increasingly weak and easily tired and found that he had to eat frequently. When he

was seen two years from the onset he was almost too feeble to stand ; there was much pigmentation and a low systolic blood-pressure (70–75 mm. Hg). His blood-sugar was 0·071 per cent. and fell, eight minutes after 2 mg. of adrenalin given intravenously, to 0·051 per cent. ; half an hour later it was 0·043 per cent. with hypoglycaemic symptoms. Three days later there was a sudden onset of convulsions, during which the blood-sugar was 0·032 per cent. and the blood-pressure 63 mm. Hg. He was given dextrose and adrenalin and recovered, but had two similar attacks the next day, and died on the fourth day in severe hypoglycaemia, his blood-sugar being 0·033 per cent. At autopsy there was tuberculosis of both suprarenal glands.

One case of suprarenal carcinoma with fatal hypoglycaemia has been reported by Anderson (No. 13). A man of 33 was admitted to hospital semi-conscious ; four months before he had temporarily lost the power of speech, and on another occasion he had spoken irrationally ; for six weeks he had been easily tired and had had double vision. Two days before admission he could not be roused in the morning and had remained semi-conscious all day, but had recovered and seemed normal for two days. Intravenous glucose restored the patient and transient glycosuria supervened, but he relapsed into a semi-comatose condition with intermittent twitching and periods of excitement, in one of which he developed rigidity of the right arm and in another unilateral Babinski's sign. The blood-pressure was 120/80 mm. Hg and the blood-sugar 0·060 per cent. The patient was given a diet containing large quantities of carbohydrate, and was able to leave the hospital. He was well for three weeks and then became violent, but glucose restored him. Two months later he was again admitted in coma ; his blood-pressure was 95/80 mm. Hg and his blood-sugar 0·069 per cent. He was repeatedly given glucose and adrenalin, but died in a few days. At autopsy the left suprarenal contained a tumour weighing 400 grm. which was histologically carcinoma of the cortex. The right suprarenal was small and fibrotic and the pancreas was extremely vascular.

Pituitary tumours. J. Wilder in 1930 published two cases of spontaneous hypoglycaemia in which there were radiological and clinical signs of pituitary tumour ; he presented the condition as a new syndrome, ' pituitary spontaneous hypoglycaemia ', and considered it to be due to lack of the secretion of the anterior pituitary leading to relative hyperinsulinism. Other cases have been reported. Cushing's patient, already mentioned, p. 118, showed a tendency to gigantism and a very low blood-sugar ; Wilder quotes four cases of spontaneous hypoglycaemia associated with proved destruction of the anterior lobe of the pituitary and six with probable pituitary lesions. Oppenheimer (1930, i) reported two further cases of acromegaly with hypoglycaemia, but without symptoms.

Wilder's first patient (No. 14) was a stout woman of 45 who had periods of semi-consciousness lasting for twelve to twenty-four 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 mm. Hg) ; the fasting blood-sugar was found to be 0·020 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 (No. 15) was also a woman, aged 55 years, who had left off eating sugar for three years because she was getting stout; she began to have attacks of odd behaviour 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 0·061 per cent., and during attacks it was 0·050, 0·053, and 0·045 per cent. The taking of sugar immediately relieved the symptoms. Her systolic blood-pressure was high (165–205 mm. Hg). She was obese and of somewhat acromegalic appearance; the X-ray picture suggested a tumour in the sella turcica and there was blurring at the edges of the optic disks.

Thyroid dysfunction. Hypoglycaemia without symptoms is frequent in myxoedema; Sigwald mentions a case in which the level was 0·064 per cent. with basal metabolism – 34 per cent. Holman reported a case in a young girl where there was a rapid fall to 0·040 per cent. with severe prostration after thyroidectomy for Graves's disease. The administration of glucose quickly restored the patient and was again successful in a relapse.

Hyperthyroidism is nearly always associated with a raised blood-sugar, but Sigwald observed two cases of Graves's disease where the level was 0·074 and 0·069 per cent. respectively.

Pluriglandular deficiency. Stenström (1926) reported two cases of hypoglycaemia in women in which the thyroid and probably other glands were reduced in activity. Pettersson reported a similar case, also in a woman, who had defective skin and nails, absence of axillary and pubic hair, amenorrhoea, low basal metabolism, low blood-pressure (90 mm. Hg), and low blood-sugar; in an attack of hypoglycaemia it fell to 0·025 per cent.

Disease of the liver. Several cases have been recorded in which destruction of the liver, and therefore of the glycogen reserves, was associated with hypoglycaemia.

Primary carcinoma of the liver accounted for two cases (Nadler and Wolfer; Crawford).

In the case of Nadler and Wolfer (No. 16), also reported by Elliott, the patient was a coloured man aged 30. A tumour of the liver was found at operation four months before his death; during the last three months of his life he had increasingly frequent and severe attacks of hypoglycaemia during which he felt exhausted, lay down, and lost consciousness; in the later attacks he was delirious; the administration of glucose always promptly relieved the symptoms. There were none of the usual signs of hepatic insufficiency, and the patient died in profound hypoglycaemia (blood-sugar 0·013 per cent.), when he was no longer able to eat and passed from one hypoglycaemic state to another. At autopsy the tumour was found to be a primary liver-cell carcinoma replacing 70–80 per cent. of the liver substance; it contained no glycogen, and the glycogen content of the remaining liver tissue, which showed atrophy and swelling of the cells, was only about 0·8 per cent. of the normal; the tumour cells contained no insulin, and the pancreas and suprarenals appeared normal, so that deficiency of glycogen rather than a relative or absolute hyperinsulinism was presumed.

In Crawford's case, another primary liver-cell carcinoma with severe hypoglycaemia, he estimated that at least 500 grm. of apparently functioning liver tissue remained ; he calculated that 300 grm. would be sufficient to carry on the functions of the liver and was in doubt as to the cause of the hypoglycaemia in his case. The glycogen content was not estimated.

Parnass and Wagner recorded the case of a child of 9 (No. 17), the subject of an hepatic tumour, whose blood-sugar showed remarkable instability ; fasting, it gave no reaction when estimated by the method of Bertrand and Michael, while after a carbohydrate meal it rose temporarily to 0·40 per cent.; glycosuria appeared and acetonuria, which had been present, disappeared, but only temporarily. An injection of adrenalin did not raise the blood-sugar. Thus an impairment of the storage mechanism was evident.

Acute yellow atrophy similarly destroys the glycogen function of the liver and brings about hypoglycaemia. Rabinovitch reported a case in a woman of 28 whose blood-sugar fell to 0·016 per cent.; autopsy showed extreme destruction of liver cells.

In fatal cases of phosphorus and chloroform poisoning (Bodansky), and of poisoning from arsenical compounds, blood-sugar values as low as 0·035 per cent. have been recorded (Cross and Blackford). MacIntosh recorded a case of phosphorus poisoning in a child of 16 months whose blood-sugar fell to 0·025 per cent. but was restored to normal by repeated injections of glucose. Similarly, in biliary obstruction the blood-sugar may be reduced (Marañon (1930)).

Besides the effects of gross destruction of the liver, it has been observed that mild chronic hypoglycaemia is often associated with hepatic defects, both in children and adults. In Cammidge's series there were thirteen cases of severe recurrent bilious attacks, six of pernicious vomiting of pregnancy, and thirty-two of cyclical vomiting in children. Marañon (1930) also observed the association of hypoglycaemia with cyclical vomiting, and it is now recognized that it probably accounts for the success of glucose therapy.

Muscular wasting. Since destruction of the glycogen stores of the liver is a cause of hypoglycaemia, it is possible that wasting of the muscles similarly deprives the body of glycogen, and McCrudden and Sargeant reported a case which might bear this interpretation. A man of 33, suffering from muscular dystrophy, had a morning blood-sugar of 0·073 per cent. which fell, after sixteen hours fast, to 0·064 per cent. After treatment the muscular power improved and the fasting blood-sugar became successively 0·080 and 0·094 per cent.

Lowered renal threshold. Reference has been made to Cammidge's observations which show that lowering of the renal threshold, which permits abnormal elimination of glucose, is common in cases of chronic hypoglycaemia. Labbé (1924) reported details of four cases, in one of which there was a family history of disturbance of carbohydrate metabolism, the patient being the son of an obese father and grandson of a diabetic. Neilsen

studied fifteen subjects of vagotonia who had hypoglycaemic reactions; seven of these had glycosuria of the renal type. The majority of patients with low renal threshold experience slight symptoms or none at all, but on several occasions symptoms have been provoked by the glucose tolerance test, at the end of which the blood-sugar fell below the fasting level; for example, Weill and Laudat reported a case in which the blood-sugar was 0·086 per cent. before the test, 0·107 per cent. at the peak of the rise, 0·048 per cent. at the end of two hours, 0·059 per cent. at three hours, but only slight symptoms occurred. Gibson and Larrimer also induced symptoms on two out of three occasions in the same patient, when the blood-sugar at the end of each test fell below the fasting value: for example, from 0·070 to 0·062 per cent.

Lactation hypoglycaemia. Lactation is a possible source of hypoglycaemia by draining the circulating glucose from the mother's blood. Widmark showed that the blood-sugar of cows is reduced during milking and is restored to normal in about twenty minutes; in women also he found a reduction, but without symptoms, the lowest observed fall being from 0·12 to 0·070 per cent.

(*Case No. 18.*) Stenström (1926) reported symptoms in a woman of 40 who was suckling a child; they were induced by a diet of fat and vegetables which was prescribed for other reasons; she had hunger, cramping pains in the stomach, tremor, and sweating; later, convulsions and stupor; on the three days of this diet the fasting blood-sugar, which had been 0·080 per cent., was 0·050, 0·040, and 0·050 per cent.; when the child was weaned there was no return of the symptoms on the same diet; this patient had pulmonary tuberculosis, which may have made her unduly susceptible to loss of glucose.

Alimentary hypoglycaemia. Starvation certainly plays a part in the production of hypoglycaemia, though it is doubtful if it is sufficient to produce symptoms in perfectly normal persons; pure alimentary hypoglycaemia is as questionable as pure alimentary glycosuria. Harris (1924) tested four patients who were 'literally starving to death', three from carcinoma of the oesophagus, and one from pyloric stenosis; there were no symptoms attributable to hypoglycaemia, and the fasting blood-sugar readings were within normal limits.

Starvation is an important factor in bringing about terminal hypoglycaemia in diabetic patients not on insulin; Joslin (1921) described three cases treated by under-nutrition, two of which were fatal. The first is a good example (No. 19).

The patient, a man of 38 years of age, had had diabetes for three years. The blood-sugar was 0·36 per cent. and acidosis was present. After four days of under-nutrition (total diet for the four days 900 calories) and two days of rigid fast the urine was sugar free and the blood-sugar 0·29 per cent. Small amounts of protein and fat were given, but no carbohydrate, and on the thirteenth day the blood-sugar was 0·050 per cent., the next day the patient was disorientated for an hour, and on the fifteenth day coma

developed unassociated with acidosis and he died in a few hours, the blood-sugar being 0·040 per cent.

Attempts have been made to lower the blood-sugar by means of a ketogenic diet containing little carbohydrate.

Inger Schröder (No. 20) gave an experimental diet of fat and vegetables to a woman medical student of 23 years of age. The diet consisted of F. 226, C. 20, P. 24 on the first day and was gradually reduced to F. 175, C. 13, P. 13 on the fourth. The subject carried out her normal active work and was greatly fatigued; she experienced tremors, nausea, palpitation of the heart on slight exertion from the second day; on the evening of the fourth day she was unusually somnolent, and on the fifth morning, after drinking a large quantity of water, she became semi-conscious; there was air hunger and acetonuria. Twelve grammes of sugar immediately dispelled her symptoms. Before the test the fasting blood-sugar was 0·094 per cent., and it gradually fell, the readings being 0·061, 0·045, and 0·052 per cent. on the last three days.

In this case exercise was probably a contributing factor, and it is possible that the symptoms were due to acidosis, which is, as Marañon points out (1930), often associated with hypoglycaemia. Begtrup and Rosling gave similar diets, and in normal persons produced only slight acidosis and slight lowering of the blood-sugar.

Organic nervous disorders are not, as a rule, associated with hypoglycaemia, although theoretically a lesion in the neighbourhood of the sugar centre would cause it. Rathery, Dérot, and Sterne studied a case in which Sigwald considers that a biological hypoglycaemia (i.e. without symptoms) was caused by a meningeal haemorrhage (No. 21).

A man 43 years of age was brought to hospital in coma. In the afternoon he had experienced a sudden headache, followed by tonic convulsions, with opisthotonos which persisted after admission. A lumbar puncture indicated meningeal haemorrhage with early haemolysis. On the third day, when the convulsions had ceased, the blood-sugar was found to be 0·054 per cent., on the fifth day it was 0·094 per cent., and for several weeks afterwards was unstable.

Oppenheimer (1930) gives a blood-sugar curve in a patient in the post-encephalitic state: after a swift rise to 0·140 per cent. it fell to 0·051 per cent.

Incidental hypoglycaemia has been reported in many diverse conditions, for example, in dementia praecox (Targowla *et al.*), neurasthenia (Nielsen), oedema (Jansen), chronic endocarditis (Goldberg, quoted by Sigwald), bronchial asthma (Malone), mumps (Mironesco, *et al.*); finally, in twelve out of thirty-three unselected, dying, patients, Schmidt and Carey demonstrated terminal hypoglycaemia of from 0·028 to 0·075 per cent.

Insulin Hypoglycaemia

By far the most common cause of hypoglycaemia is insulin injected for the treatment of diabetes; among the thousands of patients taking insulin slight symptoms of hypoglycaemia are not uncommon, and probably occur in the

majority of cases, but severe reactions are comparatively rare, especially when one considers the variability of diet and activity, the swift fall in the blood-sugar that may follow a dose of insulin, the changing susceptibility of the body, and lastly the vast possibilities for human error.

Even in patients on well-balanced diet and insulin there are certain circumstances in which hypoglycaemic accidents are likely to occur.

After the first few weeks of insulin treatment, especially in severe cases, the tolerance for sugar increases with the disappearance of acidaemia and gain in weight. If the dose of insulin is not reduced when the urine has been sugar-free for a few days, hypoglycaemia is likely to occur.

During any infection, even the common cold, sugar tolerance decreases, and larger doses of insulin are needed; in severe infections, such as carbuncles and influenza, the increase in dosage may be considerable. Hypoglycaemia occurs with recovery unless the insulin is quickly reduced.

Diabetic patients on balanced diet and insulin often have slight or moderate symptoms if they miss a meal, or even if it is unduly delayed.

Acute gastritis or enteritis, which eliminates the food before it is absorbed, acts in the same way. Two of the reported fatal cases were initiated thus. In one case the diarrhoea was severe and the autopsy revealed pancreatitis (Joslin (1928)).

In the other (No. 22) the patient reduced his morning dose of insulin to 10 units (he was on 40 units a day) on account of diarrhoea and sickness, but he took no food until he felt hypoglycaemic symptoms, when he ate an orange and telephoned to his doctor; he died before assistance could arrive (Campbell and Macleod (1924)).

Vigorous muscular exercise may bring about hypoglycaemia in the normal person, but probably only in exceptional circumstances. Levine and his colleagues estimated the blood-sugar of eleven Marathon runners in 1924: five examined before the race were within the range of normal, but six who finished in bad condition had blood-sugar levels below 0·065 per cent. at the end. They showed symptoms attributable to hypoglycaemia, such as pallor, tremor, asthenia; and the man whose blood-sugar was the lowest (0·045 per cent.) was carried in prostrate. The winner, on the other hand, who broke the world's record, finished with a blood-sugar of 0·089 per cent.; he and four others, whose blood-sugar was above 0·080 per cent. after the race, were in good condition.

In diabetics on insulin, exercise often precipitates hypoglycaemia; Lawrence (1926) described two cases in which this was very clearly demonstrated and confirmed by experiment on one of the patients, a young man, who, under similar conditions, carried out strenuous exercise on one of two days and on the other day took no exercise. On the first day he experienced severe hypoglycaemic symptoms, and his blood-sugar fell from 0·161 per cent. fasting to 0·051 per cent., while on the non-exercise day he had no symptoms and his blood-sugar remained above 0·181 per cent. It is to be noted that on the day following the exercise there was a recurrence of hypoglycaemia,

in spite of reduced insulin. The following case (No. 23) illustrates several of the conditions predisposing to hypoglycaemia:

A strong, healthy diabetic of about 40 years of age, who had been on insulin for four years, and for the last two years had taken the same dose (30 units a day, in two doses) went to the Pyrenees for a holiday. He had a long day on a mountain without mishap, and two days later undertook a severe twelve hours' climb. During the last part of the descent he had an attack of hypoglycaemia, which caused him to lose his footing and fall. He ate chocolate, but had to be helped down the remaining distance. During the night he was attacked by diarrhoea, and the next day ate little and took no insulin: on the third morning he took half his usual insulin (10 units) and a full diet, and spent a long but easy day riding a mule. In the evening he took his usual insulin (12 units) before dinner, but at the end of the meal had a slight convulsion; he was given sugar and chocolate, but soon could not swallow; he spoke slowly and thickly and was able to stagger upstairs with support. He was put to bed half-conscious and almost immediately fell into deep coma; he could not be roused and did not feel the prick of a hypodermic needle. Adrenalin had no effect, but ten hours after the onset (i.e. at 6 a.m.) the patient became conscious and soon recovered completely. He took no insulin that morning and 6 units in the evening, and had slight symptoms at 11 p.m.

This case is instructive on several points: the patient had been perfectly well for a long time on a settled dose of insulin until the glycogen reserves were exhausted by hard exercise; secondly, although diarrhoea prevented the immediate replenishment of glycogen, on the day of the attack the patient ate plenty of carbohydrate food and took no excessive exercise, yet there was no glycogen reserve, as was shown by the failure of adrenalin. The insulin taken before the final meal acted before the food could be absorbed, and chocolate and sugar failed to avert coma, although usually sweet food relieved the symptoms immediately. Recovery was presumably due to the eventual absorption of this food. In spite of reduction of insulin from 30 to 6 units he had slight hypoglycaemia on the following evening, so that even then glycogen had not accumulated; it is probable that insulin, with large amounts of carbohydrate, should have been given during and after the day's climb.

In cases of severe diabetes an especially dangerous time for the onset of hypoglycaemia is *after recovery from diabetic coma*, the large doses of insulin employed to get rid of the hyperglycaemia and acidaemia seem to exert a cumulative action, and it needs considerable experience to reduce the dose in time to prevent an excessive fall. Among twenty-four fatal cases of hypoglycaemia after insulin collected by Sigwald the greatest number (seven) followed diabetic coma.

In two cases the onset of hypoglycaemia was sudden, and the patient passed almost directly from diabetic to insulin coma.

One patient (No. 24), a woman of 29, was brought to hospital in diabetic coma (blood-sugar 0·462 per cent.); she received 135 units of insulin the 1st

day, 70 the 2nd, and 90 on the 3rd and 4th. She recovered from the diabetic coma and then suddenly lost consciousness; her blood-sugar was found to be 0·065 per cent., and she died soon after; at autopsy there was no obvious cause of death (Wohlwill).

In the case (No. 25) of a man reported by Holten, who died in hypoglycaemia twenty-four hours after the injection of only 60 units of insulin, when diabetic coma was threatening, the patient seems to have been unusually susceptible to insulin. (Quoted by Sigwald.)

Similarly, in a case reported by Beck (No. 26), a man of 48 was successfully treated for diabetic coma (blood-sugar 0·401 to 0·609 per cent.); two days after being sugar-free he developed hypoglycaemic coma after an injection of 15 units of insulin; his death was so sudden that sugar could not be given in time.

It seems probable that the glycogen stores are diminished by the failure of carbohydrate metabolism before and during diabetic coma, and that when insulin has reduced the blood-sugar to normal, there are no reserves to meet an excess of insulin. Hypoglycaemia may develop in advanced or terminal diabetes without insulin and merely from exhaustion of glycogen; it is then associated with *Acidosis*. Marañon (1930) points out that when sugar cannot be stored, insulin accentuates the acidosis by increasing the deficiency of glucose, and at the same time it produces hypoglycaemia; if glucose is given with insulin these results are obviated.

Inanition similarly reduces the glycogen stores, and in two fatal cases, one a diabetic and one a non-diabetic, death from insulin was preceded by inanition.

The first was reported by Woodyatt in 1922, when the starvation treatment of diabetes had not been superseded by insulin (No. 26). The patient was received in a state of extreme inanition and weakness and had no glycosuria; he was given a largely increased diet and a calculated dose of insulin; he developed convulsions with a blood-sugar too low to read; sugar was given and produced hyperglycaemia and gross glycosuria, but the patient died without regaining consciousness. The second case (No. 27) occurred in a woman of 27 suffering from Pott's disease of the spine and a calcified tuberculous lesion at the right apex; this patient refused food for three days, and for a further three days vomited persistently and developed acidosis. Insulin, 50 units, was given with 250 c.c. of isotonic glucose solution subcutaneously. On the following four days she received 30 units of insulin with the same glucose subcutaneously and a litre per rectum; she was also given 2 mg. of adrenalin each day. On the 4th day she suddenly became comatose; acetonuria was still present; insulin, 90 units, with 500 c.c. of subcutaneous glucose and 125 c.c. of 3 per cent. bicarbonate of soda was administered intravenously. The next day she was in profound coma with very slow respiration and severe nervous symptoms; there was neither sugar nor acetone in the urine, and the blood-sugar was 0·020 per cent. Intravenous glucose relieved the convulsions, and the blood-sugar rose to 0·149 per cent.; but the patient relapsed and died a few hours later in spite of more intravenous glucose (Sigwald).

In both these cases the lack of stored glycogen was probably the main factor; in the second case the adrenalin which was given in the early stages

would further deplete the stores; the patient may also have been hypersensitive to insulin by reason of her tuberculous lesion. In view of Underhill's experiments, the sodium bicarbonate given intravenously probably accentuated the hypoglycaemia.

Instability of the blood-sugar is a very troublesome condition generally occurring in severe cases and in emaciated patients whose store of glycogen is diminished. It becomes almost impossible to preserve the mean between hyperglycaemia and hypoglycaemia; a dose of 20 or 30 units before an ample meal reduces the blood-sugar from the neighbourhood of 0·30 per cent. to hypoglycaemic level before the next meal. Brucke instanced the case of a child of 8 who had seven severe hypoglycaemic reactions in less than a month, although her diet and insulin were under strict supervision.

In another child of the same age the fasting blood-sugar was 0·265, 0·190, 0·080, and 0·024 per cent. on different mornings, although the diet and insulin were unvaried (Heimann-Trosien and Hirsch-Kauffmann).

In one of the fatal cases (No. 28) this state of unstable equilibrium was set up. The patient, a woman of 25, was a severe diabetic, needing 50 to 60 units of insulin a day. Within fifteen days she was twice in diabetic coma (blood-sugar on the second occasion 0·450 per cent.) and twice in hypoglycaemic coma. The first of the hypoglycaemic attacks was aggravated by an injection of 40 units of insulin under the mistaken diagnosis of diabetic coma; the blood-sugar was 0·043 per cent. during eight hours of unconsciousness which ensued, and a few days later diabetic coma supervened, the blood-sugar having risen to 0·450 per cent. It was ten days after this that the second and fatal attack of hypoglycaemia developed when the patient was receiving 40 units of insulin a day (Winogradow and Steinberg).

Hypoglycaemia itself exhausts the glycogen and predisposes to another attack, even if the blood-sugar has risen in the meanwhile. Frequent small doses of insulin afford the only means of attaining an approximately normal blood-sugar, and if this is impracticable it is safer to allow a high level.

Certain complications induce a supersensitiveness to insulin; one of the most important is phthisis. It has been suggested that the great sensitiveness to insulin shown by the subjects of tuberculosis may be due to mild protein shock (*Lancet*, 1929). Two fatal cases occurred in Sigwald's series. The first was reported by Rosendahl (No. 29).

A man of 58, who had been dieted for two months for diabetes, was found to have tuberculosis of the lungs. He was very thin, and his fasting blood-sugar was 0·142 per cent. He was given a low diet, and was sugar-free, but in order to increase his diet to P. 45, F. 103, and C. 18·5, he was given 2 units of insulin each morning; the fat and protein of the diet were increased (P. 65, F. 212), and on the sixth day of insulin treatment his fasting blood-sugar was 0·087 per cent. He received his insulin as usual, and an hour later palpitation, sweating, and weakness came on. He ate 20 grm. of bread with 10 grm. of glucose, but coma developed; he recovered after 60 c.c. of a 20 per cent. solution of glucose had been given intravenously; the insulin was discontinued, but three days later the blood-sugar was 0·054 per cent. with symptoms of hypoglycaemia; glucose was again

administered intravenously and by mouth, and he recovered temporarily, but relapsed in the evening. The next morning his blood-sugar was 0·050 per cent., and in spite of a diet containing 47 grm. of carbohydrate it fell in the evening to 0·036 per cent. It became impossible to raise the blood-sugar permanently, although glucose and other carbohydrate was given freely by all methods, and he died three days later.

At autopsy both lungs were found to be tuberculous, the pancreas was cirrhotic, and there were calculi in the ducts; no glandular tissue was found, and no islets of Langerhans; the liver showed early cirrhosis and a thickened capsule.

In this case there were several conditions which may have caused or contributed to the hypoglycaemia: tuberculosis of the lungs, which may have made the patient unduly sensitive to insulin; cirrhosis of the liver, which may have lessened the capacity to store glycogen; emaciation, which further deprived the patient of glycogen, and a diet poor in carbohydrate.

It is noteworthy that the dose of insulin was extremely small—2 units a day, and that it had been suspended for three days before the fatal attack of hypoglycaemia developed.

The second tuberculous patient (Case No. 30) was a man of 30 who was admitted to hospital in 1924 with 16 per cent. of sugar in his urine, marked acidosis, and a blood-sugar of 0·357 per cent. His blood-sugar fell in four days to 0·090 per cent., but his insulin was increased from 0·5 cm. to 1 cm. to meet an increase of diet to P. 90, F. 60, C. 30. He had a hypoglycaemic convulsion, and insulin was suspended while carbohydrate intake was increased. Two days later he became excited and then semi-comatose, with nystagmus, absent reflexes, ankle clonus, and Babinski's sign; his blood-sugar was 0·027 per cent. 10 c.c. of 5 per cent. glucose was given intravenously, and repeated injections of adrenalin, but he died after being for five hours in coma.

Tuberculosis of both lungs was found at autopsy, and there was glycogen in the muscles and liver (Pemberton).

Here, as in the previous case, the diet was low and the patient was undernourished (weight 91 lb.).

Angina pectoris, arteriosclerosis, and severe heart disease are conditions in which it is agreed that the giving of insulin is dangerous. Joslin (1928) reported three cases in which death occurred; in one of them (No. 31), the sequence seemed clear:

A man who had mild angina for years died in a typical attack four days after beginning insulin treatment; no infarction was found at autopsy, but the coronary arteries were calcified and almost occluded.

A woman of 70 was brought to hospital in hypoglycaemic coma, her blood-sugar being 0·030 per cent.; she died in spite of intravenous glucose, and at autopsy a fresh infarct was found in the heart.

Gigon refers to a patient with gross disturbance of the cardiovascular system who died after the third injection of insulin.

Nicely and Edmondson mention two cases in which heart failure developed in association with hypoglycaemia. One patient with acute failure, tachy-

cardia, prostration, and pulmonary congestion, recovered after prolonged rest and the use of orange juice with reduced insulin and digitalis; the second had auricular fibrillation and recovered completely with the same treatment.

Certain conditions, which when severe are the basis of spontaneous hypoglycaemia, may in lesser degree intensify the action of insulin, for instance, in diseases of the liver such as cirrhosis, which do not entirely destroy its function, very small doses of insulin produce hypoglycaemia, and it is possible that the sensitivity of patients with severe cardiac disease and loss of compensation is due to engorgement and functional impairment of the liver. In these cases it is the lack of capacity for glycogen storage which is the most important factor (*Lancet*, 1929).

Cirrhosis of the liver was probably at least a contributory factor in a case reported by Campbell and Macleod (1925) No. 32:

A man, a chronic alcoholic, took no breakfast one morning although he had his usual 30 units of insulin. He spent an active morning, ran for a train at midday, and was taken unconscious to hospital where he died.

Addison's disease, even when not associated with hypoglycaemia, renders the individual extremely sensitive to insulin; great care must therefore be exercised in using insulin, either to increase the weight of emaciated patients with Addison's disease, or in those cases where diabetes and Addison's disease occur concurrently. Marañon (1925) cites two cases in which small doses of insulin given with ample carbohydrate produced severe hypoglycaemia:

The first patient (No. 33), a woman of 21, suffering from acute Addison's disease, died about two hours after an injection of 5 units of insulin. The second patient (No. 34), a woman of 40, had typical Addison's disease with pigmentation; she was given 10 units of insulin which produced alarming symptoms of hypoglycaemia, with a fall of blood-sugar from 0·160 to 0·044 per cent., and a fall of diastolic blood pressure to 20 mm. Hg.

A curious case (No. 35) was reported by Gellerstedt and Grill, who thought that pituitary changes may have made the patient unduly susceptible to insulin.

A man, 30 years of age, was said to be suffering from diabetes mellitus and diabetes insipidus combined. The evidence for diabetes mellitus was a high blood-sugar (0·261 per cent. when first observed, and later 0·334 per cent. with symptoms of diabetic coma), and sugar and acetone in urine. The evidence for diabetes insipidus was polyuria with low specific gravity (up to 12,000 c.c. in twenty-four hours. Sp. gr. 1,003). Autopsy revealed enlargement of the posterior lobe of the pituitary, and a 'peculiar heteromorphous composition of the cyst colloid of the pars intermedia as well as rarefaction of the colloid appearing as free droplets'.

The patient had been for some time on a liberal diet with 32 units of insulin a day, the blood-sugar varying between 0·180 and 0·100 per cent., when 'the catastrophe broke like a bolt from the blue' on June 22.

That evening his blood-sugar was 0·134 per cent. and he had 12 units of insulin as usual, and at about midnight a hypoglycaemic convulsion occurred which was checked by the administration of sugar by mouth, and adrenalin intramuscularly. The next morning he was free from symptoms, so, although his blood-sugar was only 0·086 per cent., he was given his usual 20 units of insulin; at 10 o'clock he suddenly lost consciousness, and his blood-sugar fell to 0·026 per cent. Nervous symptoms were marked, epileptiform attacks, trismus, bilateral Babinski's sign, and non-reacting pupils. He was twice given glucose per rectum (200 c.c. of a 5 per cent. solution) and adrenalin, but his blood-sugar only rose to 0·031 per cent., and he died three hours after the onset of coma.

In some cases of diabetes a lowered renal threshold develops, and there is hypoglycaemia, although glycosuria persists.

Leyton (1929) reported a case (No. 36) in a child of five and a half years who had been in diabetic coma and had required insulin; this had been suspended but resumed on account of infection; it had been gradually reduced from 36 units a day to 16, when severe hypoglycaemia developed and persisted for ten or eleven weeks with no further insulin; symptoms ceased after seven weeks, but the fasting blood-sugar was 0·060 per cent., although the diet was liberal in carbohydrates. Glycosuria was present throughout, and the renal threshold was low.

Lowered renal threshold probably accounts for some of the cases of unstable blood-sugar already discussed. The following case (No. 37) affords an example.

A woman of 56, who had been treated for diabetes for five years, was admitted to hospital in diabetic coma on five occasions, and each time had had symptoms of hypoglycaemia about a week after recovery from coma; one of these attacks was severe and the patient was unconscious for four and a half hours with Cheyne Stokes's breathing. On the preceding days the blood-sugar was 0·360, 0·374, and 0·236 per cent.; the insulin had not been increased on the day of the attack, which occurred at 11 p.m., and sugar was constantly present in the urine. The patient had persistent albuminuria, and an intermittent *B. coli* infection of the urinary tract, which may have provided the pathological basis for the permeability of the kidneys to sugar, and it was when she was admitted for observation of the renal condition that the lowered threshold became evident. In a tolerance test 1·600 per cent. of sugar was present in the urine with a maximum blood-sugar of 0·112 per cent. During five weeks no day passed without sugar being present in at least one specimen of urine, and yet moderate hypoglycaemia occurred on five occasions. The diet provided about 1,650 calories with 100 grms. of carbohydrate, and the insulin was gradually reduced from 20 units morning and evening to 15 units morning and evening: the highest fasting blood-sugar was 0·262 per cent., and the lowest 0·068 per cent. Hypoglycaemic symptoms occurred on days when the fasting blood-sugar was not at its lowest, for example, 0·143 and 0·162 per cent., whereas on the day when it was 0·068 per cent. there were no symptoms; there was often only a trace of sugar in the urine on days with no symptoms and more sugar on the hypoglycaemic days.

Ignorance and carelessness have on more than one occasion had a fatal result. One patient, who had twice been treated in hospital for diabetic coma, the last time ten days before her death, thought it was threatening

again and gave herself insulin every hour during the night—120 units in all. Glucose was given in large doses, but she died (Joslin (1928)).

Another death (Case No. 38) was due to a mistaken diagnosis, and 20 units of insulin were given when the patient was already in hypoglycaemic coma; the next day he was in deeper coma with paresis in sequence of one leg, both legs, one arm. His blood-sugar was restored by repeated injections of glucose, and indeed reached 0·220 per cent., but he died on the third day (Chabanier *et al.*).

Hypoglycaemia after suspension of insulin treatment. A few cases have been described in which fatal hypoglycaemia occurred some days after the last dose of insulin.

Jonas described a case (No. 39) in which a man of 50 had an operation for gangrene of the feet and was given 5 units of insulin at first three times and then twice a day; he refused his breakfast one day and 'insulin shock' occurred (blood-sugar 0·063 per cent.), and the insulin was suspended. Eleven days later he became delirious, his blood-sugar was 0·030 per cent., and he died in spite of the administration of sugar.

This case occurred in the days of low carbohydrate diet, and is probably analogous to the cases of terminal hypoglycaemia in untreated diabetes. In the tuberculous patients (Nos. 29–30) the insulin had been suspended for three days and two days before the onset of hypoglycaemia.

Diagnosis

The diagnosis is to be considered under two aspects:

In the *non-diabetic* the great diagnostic criterion is the time of the onset of symptoms, viz., early in the morning or before meals, and the almost immediate relief after taking food. Even if the symptoms themselves do not seem to fit in exactly with those described, and even if the patient's disability amounts only to weakness and fatigue, this definite relationship to food is enough to warrant an estimation of the blood-sugar which will clinch the diagnosis.

As may be supposed from the list of symptoms many conditions simulate hypoglycaemia.

Organic nervous diseases, such as those due to cerebral vascular thrombosis, which give rise to hemiplegia or coma are obvious difficulties, but the paralyses of hypoglycaemia are generally transient.

Cerebral tumour was the first diagnosis in a case reported by Womack, Gnagi, and Graham (No. 6) of a man of 44 who had attacks of mental confusion, loss of memory, and transient loss of consciousness. He proved to have an adenoma of the pancreas and spontaneous hypoglycaemia. All his symptoms disappeared after excision of the tumour.

Encephalitis was considered a possible diagnosis and a lumbar puncture was performed in the case of McClenahan and Norris.

(*Case No. 40.*) A man of 41 was brought into hospital unconscious and regained consciousness in an hour and a half. The next day, however, he was again in coma and his blood-sugar was 0·040 per cent., while the sugar in the cerebrospinal fluid was 0·020 per cent. A history was obtained of attacks of loss of memory during the past six months, lasting about an hour and a half and recovering after food. Glucose by mouth, per rectum, and intravenously was unavailing: broncho-pneumonia developed and the patient died. The blood-sugar on the three days during which the coma lasted was 0·040, 0·042, and 0·038 per cent. At autopsy an adenoma of the pancreas was found.

Epileptiform attacks may be indistinguishable from true epilepsy; for instance, in the case reported by Carr and others (No. 5), and even more dramatically in three cases described by Nielsen and Eggleston in which typical epileptic fits began between the ages of 20 and 30 years; one patient had more than 100 attacks of grand mal and many of petit mal; in each case the blood-sugar was found to be low, and a régime, which included frequent feeds and the administration of suprarenal extract by the mouth, abolished the attacks; one of the patients neglected his early morning glass of orange juice and an attack of major epilepsy occurred. The blood-pressure in one of the cases was low at the outset (98/58 mm. Hg) and was raised to 112/66 mm. Hg during treatment; the curve of the glucose tolerance test also rose to higher levels. Four of Cammidge's cases of chronic hypoglycaemia were believed to be suffering from mild epilepsy (1903).

Hypoglycaemia has been recorded in true epilepsy, where glucose therapy may increase the blood-sugar but has no effect on the fits (Targowla *et al.*) so that the therapeutic test is in these cases a more valuable aid to diagnosis than an estimation of the blood-sugar.

The symptoms of hypoglycaemia often resemble psychoses, such as mania, obsessions, and melancholia; Oppenheimer (1927) cites instances, and Cases 13 and 15 are examples; Sjögren and Tillgren described three cases of confusional violence; one man became unmanageable on several occasions; he threw things about, shouted 'I will murder you', bit, fought, and almost threw himself over the banister; another rushed out of the ward and upset a food-wagon, and a third threatened a fellow patient with a knife. The transitory nature of the unnatural behaviour is an important point in the diagnosis.

Functional nervous disorders such as neurasthenia and hysteria may be closely imitated in hypoglycaemic states.

A young diabetic woman on insulin (No. 41)[3] had attacks of stupor, one of which lasted for three days; the first diagnosis of diabetic coma was revised after an estimation of the blood-sugar, which showed a moderate blood-sugar content. As the attacks were associated with jealousy and family antagonism they were considered to be hysterical, and the patient was sent to a home for nervous disorders, where she was found to have schizophrenic symptoms with

[3] I am indebted to Dr. Helen Boyle for the history of this patient before the hypoglycaemic attack.

a paranoid strain. When an attempt was made to induce her to take up an employment the attacks returned and were thought to be due to a neurotic refusal to face the world; one occurred at 2 p.m. one day when the patient returned late for lunch from a secretarial college: she lay in coma for two hours; the blood-sugar was found to be 0·056 per cent. and an injection of adrenalin immediately restored consciousness. In this case there were three possibilities, hysteria, diabetic coma, and hypoglycaemia.

Intoxication by alcohol and narcotics are almost impossible to distinguish except from the history; one of Cammidge's patients was thought to be a victim of secret drinking although he was really a total abstainer.

If the patient is first seen in convulsions, uraemia, cholaemia, and eclampsia must be considered as well as diabetic coma if it is not known whether the patient has diabetes or not.

In the case of the known *diabetic* the question does not usually arise unless the patient is unconscious or semi-conscious, and the main problem is to decide between diabetic and insulin coma. In the milder stages the patient himself usually knows whether hypoglycaemia is threatening. The following distinctions between the two states may be made: the onset of diabetic coma is gradual and is usually preceded by drowsiness, loss of appetite, and deeper respirations, whereas hypoglycaemic coma may develop in a few minutes.

In diabetic coma the smell of acetone in the breath can generally be appreciated. The skin and tongue are dry in diabetic coma and the patient often dehydrated; in insulin coma the skin is clammy and the tongue moist. The ocular tension is lower in insulin than in diabetic coma. The respiration is deep and slow in diabetic coma, air hunger is present; in insulin coma the respiration is usually shallow; occasionally there may be bradypnoea, as in a case reported by Sigwald (No. 27) where the rate fell to five per minute, but the rhythm was different from the sighing respiration of air hunger; it was violent and explosive with intervals of apnoea lasting for about twelve seconds.

The blood-pressure is often raised in hypoglycaemia and low in diabetic coma, but the difference is not constant, and in hypoglycaemia associated with Addison's disease the tension is of course low.

Examination of the urine, if obtainable, should be diagnostic, but it can mislead. Sugar is usually absent in insulin coma and abundant in diabetic coma, but the presence of sugar does not exclude a diagnosis of hypoglycaemia because in cases of instability, when the blood-sugar varies rapidly, the urine may have been secreted before the onset of hypoglycaemia and may contain sugar; or the renal threshold may be low as in Case 37. On the other hand, diabetic coma may occur with profound acidosis in the absence of glycosuria.

Ketone bodies—acetone and diacetic acid—are always abundant in diabetic coma and are usually absent in hypoglycaemia, but again there are exceptions. It has been pointed out (p. 142) that in advanced diabetes

where there are no glycogen reserves acidosis may be associated with hypoglycaemia. Labbé (1928) recognized that both sugar and ketones may be present.

The nervous signs are not, in general, diagnostic, but stress has been laid on the presence of the Babinski response in insulin coma and its absence in diabetic coma. If present, it is a reliable indication, though it is to be remembered that diabetic coma may be complicated by a pyramidal tract lesion or by uraemia or other intoxication causing a Babinski reflex (Hart, Price-Bond (1929), Hawthorne (1929)). On the other hand, the reflex is not present in all cases of insulin coma, especially in the less severe stages. The writer observed a patient who lay completely unconscious for over two hours but was sufficiently responsive to resent by slight movements the passage of a catheter; no urine was obtainable, but the blood-sugar at the end of the period was 0·056 per cent. The plantar reflexes were tested more than once; the left was definitely flexor, the right 'doubtful'.

The pupils are at about mid-dilatation and the reaction to light is absent or sluggish.

In all doubtful cases an estimation of the blood-sugar is the final appeal; if this is unobtainable it is wise to treat the disease as if it were insulin coma, with glucose or adrenalin; if the diagnosis is correct the patient usually improves within a quarter of an hour; if not, large doses of insulin can be given.

Prevention and Treatment

Spontaneous hypoglycaemia, when the symptoms are slight, can be averted by giving frequent meals, rich in carbohydrate; an orange drink during the night or early in the morning is often sufficient. Seale Harris (1932) considers that a diet relatively poor in carbohydrate and rich in fat, with moderate protein, is more effective, and cites a case when this was so; food is taken every two or three hours and during the night, if necessary. Suprarenal extract by the mouth was given in three cases as an adjuvant (Nielson and Eggleston), but does not appear to have much advantage over diet alone, unless the blood-pressure is low.

When the symptoms persist and increase, the question of *surgical intervention* is to be considered; it has been carried out in nine cases, and resulted in complete relief of symptoms in four. In two of the cases carcinoma of the pancreas was found; one was inoperable (Case 2), but in the other case a small tumour was removed, and a month later the sugar tolerance curve was normal (No. 4). In three cases an adenoma of the pancreas was excised with complete success (Nos. 5 and 6 and a case mentioned by Cushing (1930)).

In four cases (Nos. 9, 10, 11, and 11A) the pancreas appeared normal, and partial pancreatectomy was performed, but without permanent benefit. Surgery offers most hope of success in cases of adenoma of the pancreas, but

these tumours are rare and almost impossible to diagnose; in view of the good results in the three cases mentioned it would seem that exploratory laparotomy is justifiable in cases of severe and increasing spontaneous hypoglycaemia, provided that lesions of the adrenals or pituitary can be excluded. Partial resection of a normal pancreas does not seem to be worth while. Two-thirds of the substance (22·5 grm.) was the largest amount resected (Finney and Finney).

The prevention of the onset of hypoglycaemia in *diabetic patients* treated with insulin needs attention to the following points:

(1) The balance of insulin and diet should be reviewed from time to time and the fasting blood-sugar estimated: when the patient is not under observation he should be warned to reduce the insulin if the urine is persistently sugar-free; slight glycosuria is safe, unless the renal threshold is low.

(2) Care should be taken to reduce the insulin soon enough in recovery from coma and from infections; it is wise to give glucose with insulin in treating diabetic coma, 1 grm. of carbohydrate for each 3 units of insulin (Spriggs).

(3) When exhaustion of glycogen stores is likely, as in states of inanition and starvation or after prolonged exercise, glucose or carbohydrate food should be given liberally with large doses of insulin.

(4) After manifestations of hypoglycaemia, however slight, insulin should be discontinued, reduced, or guarded by abundant carbohydrate until the balance is re-established; the last course is probably the best, as it promotes replenishment of glycogen stores (cf. Case No. 23).

(5) All diabetics on insulin should carry sugar about with them, and eat it at the first warning of symptoms.

(6) Great care must be taken in the administration of insulin to patients suffering from a complication likely to make them abnormally susceptible to insulin intoxication; especially cardiovascular diseases, tuberculosis, and suprarenal deficiency.

In an *actual attack of hypoglycaemia* the indication is to give sugar in any form. If the patient can swallow he should eat sugar, barley sugar, or any sweet food; a sweet drink such as orange juice or lemonade and sugar is absorbed more quickly, but should not be dilute; the taking of any food relieves slight symptoms, and an ounce of sugar or its equivalent is usually ample in severer cases.

When the patient is in coma the intravenous injection of glucose is by far the most certain method of introducing sugar; 10 grm. in 50 to 100 c.c. of sterile saline solution is an adequate dose (Spriggs); Sigwald considers it dangerous to give much fluid, and recommends 10 to 20 c.c. of a 20 or 30 per cent solution.

Subcutaneous glucose in isotonic solution may be given; rectal glucose, $7\frac{1}{2}$ per cent., is often administered, but Harris (1932) considers it futile and cites evidence to show that it is not absorbed; in Case No. 35 glucose per

rectum hardly raised the blood-sugar, but in Case No. 37 it was the only treatment used, and recovery ensued, though slowly. If it is impracticable to give intravenous glucose, it is probably best to introduce a strong solution directly into the stomach by means of an oesophageal tube.

Sometimes death occurs in spite of doses of glucose, which should be amply sufficient to restore the blood-sugar; for example, a child aged 8 received 107 gr. of glucose, the greater part intravenously, but the blood-sugar fell during treatment from 0·093 to 0·052 per cent. (Heimann-Trosien and Hirsch-Kauffmann). In some cases the blood-sugar can only be raised temporarily, and this occurs especially in spontaneous cases with increased secretion of insulin, but it may happen in diabetics, especially if there are complications; for example, in Rosendahl's tuberculous Case No. 29, 55 grm. of glucose caused the sugar to rise from 0·042 to 0·060 per cent., but it fell shortly to 0·048 per cent., and the patient died. A case described by Root (No 42) illustrates the difficulties encountered when there is infection.

A woman of 51 had a gangrenous toe and pyrexia (101° F.–102° F.). The fasting blood-sugar, which had been 0·40 per cent. on admission, fell to about 0·20 per cent., and the urine became sugar-free on 60 units of insulin a day; an attempt was made to bring the blood-sugar to normal, as the pyrexia persisted after amputation of the toe; and a dose of 80 units three times a day (240 units in twenty-four hours) was reached by rapid increase; the blood-sugar suddenly fell to 0·015 per cent. The leg had been amputated three days before, and the temperature was lower, so that recovery from infection may have made the patient less resistant to large doses of insulin.

Uraemia supervened, as it often does in diabetic coma, and probably contributed to the fatal result. Two intravenous injections of glucose were given, after each of which consciousness returned, but the patient died in a third relapse before glucose could be administered. The danger of giving large doses of insulin when the blood-sugar is approaching normal is apparent here.

Another disturbing occurrence is that several patients have died although the blood-sugar was restored to normal or above; this was so in the first case of death from insulin intoxication reported from Scandinavia (Dahl).

(*Case No. 43.*) A woman of 52 was admitted in the early stages of diabetic coma with a blood-sugar of 0·385 per cent., the urine was loaded with sugar and acetone and contained albumin; she recovered well with moderate doses of insulin, and was sugar-free on the following day with a blood-sugar of 0·144 per cent., though acetone was present until the ninth day of treatment. Glycosuria occurred intermittently during the week, and the insulin had been increased from 15 units in three doses on the fourth day to 35 units on the eighth (10.15.10). On the morning of her fatal attack the blood-sugar was 0·165 and the urine free from sugar and acetone. She had 10 units of insulin early and 15 before her midday meal, but did not eat her bread; three hours later she was in deep coma with a blood-sugar of 0·025 per cent.; seven hours after the onset of coma the blood-sugar had been raised to 0·380 per cent. after injection of adrenalin and sugar, but she died without recovering consciousness nineteen hours after the onset, her blood-sugar being 0·089 per cent. two hours before death.

In Chabanier's case (No. 38) the blood-sugar was raised to 0·26 per cent., and yet death occurred. In cases such as these it is probably not the low blood-sugar that brings about the fatal result (cf. p. 121).

The injection of adrenalin, 15 minims of a 1 in 1,000 solution, is a rapid method of treatment, provided that the glycogen stores are not exhausted. Pituitrin 1 c.c. is equally effective.

Caffeine has been found beneficial. Popper and Jaboda injected 1·4 grm. of caffeine sodium benzoate.

The injection of calcium chloride is said to be of use in the treatment of convulsions, and the administration of calcium lactate in their prevention.

Danger of accidents. Should insulin patients drive motor-cars? is a question that has been raised recently in Scandinavia (*Lancet*, 1932). A Danish lorry driver, aged 25, having taken his insulin at 8 a.m., was called out before breakfast; he took some food with him, but partly lost consciousness while beginning to eat it, and his lorry charged a stationary vehicle. Such accidents are not common but are always possible, especially with patients who need large doses of insulin or whose blood-sugar equilibrium is unstable. Professor Holst and Dr. Müller, who published a memorandum in the report of the Norwegian Medico-legal Commission, recommend that insulin patients should not be allowed to drive taxis or motor omnibuses, and that permission to drive a car should be dependent on a medical certificate that the insulin balance is regulated and steady, and is understood by the driver.

Other occupations may be dangerous either for the patient or to others; Sonne reports the case of a man in the railway service who on many occasions was found 'wandering senseless about the railway grounds' in attacks of hypoglycaemia.

Although diabetics on insulin are able to carry out almost any work or profession, they are not suitable for strenuous occupations where a momentary loss of control is fatal—for instance, that of engine-driver, air pilot, or racing motorist.

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