SOME NEUROLOGICAL MANIFESTATIONS OF ENDOGENOUS HYPOGLYCAEMIA*

BY

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Hypoglycaemia has been recognized as a clinical entity for only about fifty years, although some of the mechanisms by which it may be produced must have been operating throughout the ages. After the introduction of insulin for the treatment of diabetes in 1922 insulin "reactions" were observed for the first time, and Seale Harris then realized that he had seen patients with similar symptoms who were not being given insulin; thus in 1924 he introduced the concept of "spontaneous" hypoglycaemia (Harris, 1924), and since then papers too numerous to quote have been devoted to the subject.

I have used the term "endogenous" rather than "spontaneous" because it is more accurate, since there must always be a reason for the development of hypoglycaemia even if it cannot be fully understood, and endogenous hypoglycaemia may be defined as the production of an abnormally low blood-sugar level by any means other than the exogenous administration of insulin, usually giving rise to symptoms or, less often, to physical signs.

My observations have been limited to those patients in whom hypoglycaemia appeared to be the primary factor in the production of symptoms, thereby excluding hypoglycaemia which is part of a complex biochemical syndrome, as in gross liver disease or endocrine disorders and in other uncommon conditions. There remain for consideration three main types of endogenous hypoglycaemia—namely, organic hyperinsulinism resulting from the presence of functioning pancreatic islet-cell tumours, hypoglycaemia arising as a sequel to various gastric operations, and psychosomatic hypoglycaemia.

Diagnostic Criteria

In our present state of knowledge establishing a diagnosis of endogenous hypoglycaemia must rest ultimately on blood-sugar estimations. It seems to be beyond doubt that there is no critical level at which the clinical manifestations of hypoglycaemia appear, and the values differ from one person to another and in the same individual from time to time. The production of symptoms seems to be determined either by abnormally low blood-sugar concentrations (usually in the region of 55 mg. per 100 ml. or less) or by an extremely rapid fall, such as 100 mg. per 100 ml. or more in thirty minutes, without the production of unusually low levels. There is no constant relationship between the blood-sugar concentration and the severity of the symptomatology.

Moreover, it was stressed by Richardson and Russell (1952) that if the manifestations are severe and prolonged, as in the coma produced by an islet adenoma, the blood sugar may return to normal or even rise above normal before the patient recovers, and this can easily lead to diagnostic errors. The glucose-tolerance test may be a valuable aid in the diagnosis and differentiation of clinical hypo-

glycaemia, but even if prolonged for six hours it is often found to be normal in a patient who from time to time may suffer from hypoglycaemic episodes. On the other hand, the findings may be consistently abnormal in the absence of symptoms, as, for example, in most post-gastrectomy patients; therefore the results must be interpreted with caution.

Personal Experiences

I have had the opportunity of studying the clinical manifestations in 20 patients who came to my notice while I was at the Leeds General Infirmary in 1952 and in 1954-5; earlier observations had been made on some of them. Space does not permit detailed presentation of their case histories.

In the first group were seven patients with organic hyperinsulinism; two of them had islet adenomata which were removed surgically, one with the complete remission of all symptoms, though unfortunately the other died post-operatively. The remaining five were suspected of having insulin-secreting tumours on the basis of the severity of their clinical symptoms together with the finding of characteristically low fasting blood-sugar values; furthermore, in three, hypoglycaemic levels were demonstrated in the presence of symptoms which were then promptly relieved by the administration of glucose or adrenaline (Whipple, 1944). Two of them were subjected to laparotomy, but no pancreatic abnormality was found, and one man refused to submit himself to operation; the remaining two were the oldest and the youngest of the whole series, aged 78 and 5 years respectively, and on these grounds laparotomy was withheld.

The second group consisted of five patients who had had subtotal gastric resections for peptic ulceration, together with a sixth upon whom gastro-enterostomy and vagotomy had been performed, and it is probably significant that in addition they were all obvious neurotics. For the most part their symptoms consisted of relatively mild postprandial "attacks" with spontaneous recovery, though, contrary to the generally accepted view that severe manifestations do not arise from hypoglycaemia as a sequel to gastric surgery (Conn and Seltzer, 1955), sometimes there was sudden loss of consciousness, and one patient had a prolonged phase of coma. Furthermore, in these six examples the latent interval after operation and before the onset of symptoms was found to vary from two months to ten years. In such patients there is an exaggeration of the normal response to the ingestion of food, especially if the carbohydrate content is high, and this is illustrated by the characteristic "lag" or reactive glucose-tolerance curve (Lawrence, 1936).

In the third group, which consisted of seven examples, it appeared that psychological factors in patients of neurotic and unstable personality gave rise to clinical hypoglycaemia in the absence of organic disease or previous surgical intervention; therefore the term "psychosomatic" seems to be more appropriate than the commoner nomenclature of "nervous" or "functional" hypoglycaemia. In these patients the clinical manifestations were usually mild and transient, though two had convulsions and one had prolonged phases of confusion. The precise mechanism is complex and uncertain, but it seems that symptoms may arise either because the postprandial rise of blood sugar stimulates an excessive release of insulin, which is followed by a reactive phase of hypoglycaemia, or because there is instability of the nervous mechanisms controlling insulin secretion. The latter explanation would seem to be the basis of the oscillating levels which were seen towards the end of a six-hour glucose-tolerance test in four of these patients and which were noted in similar examples by Prunty (1944). In psychosomatic hypoglycaemia, like that arising after gastric operations and as opposed to organic hyperinsulinism, the fasting blood-sugar level is within normal limits and symptoms do not usually arise in the fasting state.

I have analysed and attempted to group the various manifestations that were observed in these 20 patients with endogenous hypoglycaemia. Because of the metabolic

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limitations which are peculiar to nervous tissue, they fall predominantly into the neuro-psychiatric sphere, but the reactive mobilization of adrenaline, which normally occurs in response to the hypoglycaemic state, also produces symptoms which are often inextricably combined; these take the form of vague sensations of "weakness" and anxiety, together with sweating, palpitation, pallor, and nausea.

Disturbances of Consciousness

The largest group of symptoms, and the only one which involved all the patients under review, included all varieties of disturbance of consciousness. Some of these were difficult to define precisely, consisting of a sensation of "faintness" or "light-headedness," although there was no unequivocal example of a typical syncopal attack. More severe disturbances consisted of phases of confusion, with or without automatism and amnesia; in two cases these were identical with the hysterical fugue in that the patient carried out highly complex and lengthy procedures with subsequent amnesia, but more commonly there were shorter phases of amnesia associated with simpler automatisms, frequently taking the form of what are usually regarded as psychomotor epileptic seizures of temporal lobe origin. It is interesting and impressive that many of the other symptoms exhibited by the patients under review are generally thought to arise from disturbance of function in the temporal lobe; these included hallucinations of vision, taste, and smell, lip-smacking, circumoral paraesthesiae, and probably also vertigo.

In 15 cases there were attacks of sudden unconsciousness with or without an aura or complications such as injury or incontinence. It was often impossible to decide from the evidence of lay observers whether there were tonic or clonic phases or cyanosis, but at least four had undoubted major epileptic fits which appeared to be basically determined by hypoglycaemia, and in two of these there was little in the patient's history to suggest that the attacks were anything other than those of so-called "idiopathic" epilepsy. The maximal effect of hypoglycaemia on consciousness is the production of deep and prolonged coma, lasting for several hours or days, and this occurred in three cases; two of these were suspected of having islet-cell tumours, but the third was remarkable (as stated above) in that coma resulted from post-gastrectomy hypoglycaemia. It is easily understandable that the phasic activity of an insulin-secreting tumour may produce prolonged hypoglycaemic coma, but it is more difficult to understand the mechanisms whereby hypoglycaemia arising after gastric operations may do so, for one would expect the mechanical effects of a surgical procedure to be constant.

It has been shown by Lawrence, Meyer, and Nevin (1942) that hypoglycaemic coma may cause irreversible cellular necrosis, which is maximal in the cortex, basal ganglia, and Purkinje cells of the cerebellum, probably arising because of cerebral anoxia. This may lead to permanent neurological sequelae if the patient recovers, though it is also possible for such coma to be totally reversed even after several days.

Pyramidal and Extrapyramidal Syndromes

Another group of neurological disturbances included signs which are generally accepted as being of pyramidal or extrapyramidal origin. Hemiparesis was observed in one patient who, at the same time, had an ipsilateral homonymous hemianopia all of which was rapidly reversed by intravenous glucose. How such unilateral and paralytic phenomena can result from hypoglycaemia is unknown, and few theories are to be found in the literature, but it may be that there is some anomaly of the cerebral arterial supply which is adequate under normal circumstances but which becomes inadequate in the anoxic state produced by severe hypoglycaemia. A more prolonged hemiplegia, persisting for three days, was seen in another patient, and in this case there was the simultaneous appearance of choreo-athetoid

movements involving the opposite limbs. Such bizarre combinations of symptomatology as this are, however, not uncommonly seen in the hypoglycaemia produced by insulin therapy for psychotic states (von Angyal, 1937; Golden, 1937).

Cerebellar Manifestations

Ataxia, dysarthria, and sometimes nystagmus, all of which may result from disturbances of cerebellar function, have been observed as transient phenomena in four patients. It is well known that cerebellar defects may arise from toxic causes, as in acute alcoholism or intoxication by the hydantoins, and, since it seems that there is always some disturbance of consciousness in patients with hypoglycaemic symptoms, it will be seen that the combination of confusion and a cerebellar disturbance might easily be mistaken for the symptoms of alcoholic intoxication, as was the case in two of these patients. Hence this aspect of the subject has potential medico-legal importance.

Visual Disturbances

The disturbances of vision which have occurred in this series include hemianopia, diplopia, and macropsia; in one case complex visual hallucinations often occurred at the onset of a hypoglycaemic attack. Homonymous hemianopia has been seen only once and in association with an ipsilateral hemiplegia, which suggests that the underlying disturbance of cerebral function was of a very localized kind. Diplopia always has a wide nosological background, and it would be impossible to speculate on the ways in which it could be produced. Macropsia is even more difficult of assessment, though it has been observed as part of the aura of migraine and epilepsy, and complex visual hallucinations are often seen in association with disorders of the temporal lobes; several authors (quoted by Kalinowsky and Hoch, 1952) have observed similar phenomena both in patients undergoing insulin therapy and in experimental hypoglycaemia.

Rotatory Vertigo

The final symptom remaining for discussion is rotatory vertigo, and this is perhaps the most significant finding. This manifestation, arising in endogenous hypoglycaemia, does not appear to have previously been described (a view confirmed by Dr. C. S. Hallpike, 1955, personal communication), though de Morsier and Bersot (1938) found that "vertigo or a feeling of gyration" was produced during insulin therapy together with other symptoms of parietal and temporal lobe origin.

Throughout the series transient vertigo was excluded as a possible hypoglycaemic symptom in the presence of deafness, tinnitus, or middle-ear disease, but there is no doubt that attacks of rotatory vertigo occurred in four of the patients under review, and that this symptom arose in each of the aetiological groups. The vertigo was either subjective or objective and sometimes occurred so precipitately that the patient fell to the ground; the duration was usually from a few minutes to about an hour, though sometimes it was more prolonged, and it was on occasions associated with nausea and vomiting. In one patient recurrent attacks of rotatory vertigo were the first expression of the hypoglycaemic state and in the three others it appears to have constituted part of the aura of an epileptic attack. Consciousness must always be disturbed during an attack of severe vertigo to the extent that the patient is totally preoccupied with his symptoms. It has always been known that rotatory vertigo may be associated with transient loss of consciousness, and this has been thought to apply to vertigo apparently of vestibular origin, but it is suggested that in the light of the present finding such a view may call for some reassessment.

The precise level of neural activity at which hypoglycaemia operates in the production of rotatory vertigo can

only remain speculative. The absence of deafness and tinnitus makes it unlikely that the disturbance of function is arising primarily in the labyrinth, and it would seem more probable that it results from a biochemical disturbance operating on the temporal lobes; weight is lent to this view by the cortical stimulation work of Penfield and Rasmussen (1950), who found that a feeling of "dizziness" could be produced by stimulation in various parts of the brain, especially when this was subcortical, and they concluded that movement of the whole body in space is "represented" in the first temporal convolution. Penfield and Jasper (1954) made further references to the same experiments in cortical stimulation and described a patient in whom clockwise rotatory vertigo associated with nystagmus was produced by stimulation of the parieto-occipital cortex, though in this case there were associated visual hallucinations. I have not had the opportunity of observing a patient during an attack of vertigo, and it is therefore impossible to say whether there was nystagmus or ataxia of the limbs in these examples.

Conclusions

It is apparent both from personal observations and from a study of the literature that the clinical manifestations of hypoglycaemia are protean. It has usually been accepted that humoral mechanisms would operate on the central nervous or any other system in a symmetrical fashion, but it is clear from observations in hypoglycaemic states that this is not always true. Himwich (1951) suggested that the effects of hypoglycaemia are largely centred on phylogenetically new parts of the nervous system, but this is not strictly accurate, and it seems that lowering of the blood-sugar concentration has varying effects which cannot be simply interpreted in terms of physio-anatomical "levels" or concepts of "localization" as we understand them to-day.

Summary

The aetiology of endogenous hypoglycaemia (as the essential factor in the production of symptoms) is considered under three main headings; thus it may result from islet-cell tumours, as a sequel to gastric surgery, or from psychosomatic mechanisms.

The terminology and criteria for diagnosis are briefly discussed. Twenty case histories are outlined, and an attempt has been made to analyse and group the neurological manifestations observed.

All these patients experienced disturbance of consciousness at some time, though varying in degree from confusion to deep and prolonged coma; sudden loss of consciousness and major epileptic fits occurred.

Many episodes suggestive of disturbance of function arising in the temporal lobe were encountered, including psychomotor seizures (often with automatism and amnesia), hallucinations of vision, taste, and smell, lip-smacking, circumoral paraesthesiae, and vertigo.

Both pyramidal and extrapyramidal syndromes in the form of transient hemiparesis and choreo-athetosis were observed.

Cerebellar manifestations (which are sometimes mistaken for alcoholic intoxication) may arise, and also visual disturbances such as diplopia and hemianopia.

Perhaps the most significant finding is that rotatory vertigo was determined by endogenous hypoglycaemia, sometimes as the presenting symptom, and the probable physio-anatomical basis is suggested.

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PREGNANCY COMPLICATED BY DIABETES MELLITUS

A REVIEW OF 119 CASES

BY

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When insulin was introduced it was confidently hoped that there would be a decrease in both maternal and foetal mortality in diabetes mellitus. This hope has only been partially fulfilled. The number of maternal deaths has shown a marked decline, and death of a pregnant diabetic woman seldom occurs to-day. In contrast, the foetal mortality, while showing some improvement, still remains discouragingly high. Henley (1947) reviewed the reports in the world literature of 1,269 cases of diabetic pregnancies. The total foetal mortality was 37.6%. White (1952) collected 640 cases from the literature since 1940. The average foetal mortality was 34.8%; it varied from 8% (in a very small series) to 70%.

It has been my impression that the chances of foetal survival could be appreciably increased by more careful and detailed supervision, and with this idea in mind a review of a series of diabetic pregnancies treated in the Royal Maternity Hospital, Belfast, during the years 1940-55 was carried out.

The records of this hospital show that during the 16 years mentioned 89 women with diabetes mellitus had 119 pregnancies (Table I).

TABLE I

	Pregnancies	Primigravidae	Multigravidae
1940-50	67	18	49
1951-5	52	15	37
1940-55	119	33	86

The Royal Maternity Hospital is attached to a large teaching hospital (Royal Victoria Hospital), which provides a diabetic clinic treating over 400 new patients a year. Practically all pregnant diabetics attending this clinic are referred to the Royal Maternity Hospital.

Review of the literature suggests that the number of pregnant diabetics is increasing. There would appear to be little impairment of fertility in adequately treated diabetic women. In the present series, 37 patients out of a total of 40 who were known diabetics at the time of marriage conceived within two years; 26, or 70%, conceived within one year. My experience would agree with that of White (1952), who claims that "the diabetic