# NARCOLEPSY AND HYPOGLYCAEMIA*

By

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FOR some years now it has been recognized that the symptoms induced by hypoglycaemia may resemble narcolepsy. Cases of islet-celled pancreatic adenomas simulating narcolepsy have been described by Harris (7), Delay (4) and Wyke (18). The resemblance may be a superficial one, however, and Wyke observed in his case during a "sleepy attack" that "the EEG pattern bore no resemblance to that of natural or artificial sleep". In a more recent paper Ziegler and Presthus (19) described thirteen patients who showed normal EEGs at blood glucose levels (induced by fasting and intravenous insulin) of from under 15 mg. per cent. to 54 mg. per cent. In eight of these patients there were no clinical symptoms; in the remaining five patients the symptoms were described as follows: "feel like a ton of lead", "warm and sleepy", "tired", "drowsy and sweaty" and "dizzy and tired". It seems, in fact, that the clinical description of drowsiness in hypoglycaemia may correspond either to no EEG changes or to various degrees of slowing rather than to the typical recurrent light sleep patterns characteristic of narcolepsy. It will be recalled that hypnosis too is ushered in by a sense of drowsiness but that the EEG changes are not those of sleep (1, 2, 5). Many hysterical trance states—often loosely, and unfortunately, described as narcolepsy—come into this category. In short, it is apparent that all that sleeps is not narcolepsy (6, 12, 13, 14).

In this paper we should like to describe the EEG changes occurring under hypoglycaemia in five cases of true narcolepsy. In a previous paper devoted mainly to the clinical aspects Smith (13) drew attention to an apparent alerting effect in the EEGs of two narcoleptics who were rendered hypoglycaemic by intravenous insulin (Cases 1 and 2 below). Since then three cases have been added and we would like to describe and discuss the phenomenon in more detail.

## METHOD

The method, which was developed by Hoffer (9) as part of a homeostatic battery of tests in psychiatric patients, consists in injecting intravenously one unit of soluble insulin per eight pounds body weight in the fasting subject. Prior to the injection the EEG is taken for twenty minutes; afterwards blood

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is taken (for glucose) four times at ten minute intervals and the EEG changes are recorded. About fifty minutes after the insulin injection hypoglycaemia is terminated by the I.V. injection of 50 c.c. 33⅓ per cent. glucose and further EEG recordings are taken for twenty minutes following which the patient is returned to the ward.

The EEG examinations were carried out on a Grass Model 3D console eight-channel apparatus. Silver disc electrodes applied with collodion were used. Parallel E.K.G. examinations were recorded simultaneously on lead II or lead III. No sedatives or stimulants were given for the preceding twenty-four hours.

## Results

The EEG and clinical changes under hypoglycaemia were as follows:

*Case 1.* Female, aged 27, with narcolepsy, cataplexy, sleep hallucinosis and paranoid psychosis.

The pre-insulin EEG showed no abnormality. It was difficult to keep the patient awake during hyperventilation but when this was done no abnormality appeared. Seventeen units of soluble insulin was given at 8.55 a.m. Blood glucose findings were as follows: 8.45 a.m. (fasting) 108 mg. per cent., 9 a.m. 88 mg. per cent., 9.10 a.m. 50 mg. per cent., 9.20 a.m. 38 mg. per cent., 9.30 a.m. 64 mg. per cent. I.V. glucose was given at 9.37 a.m.

From 8.55 a.m. on it was noted that she was not nearly so drowsy. Some drowsiness was noted at 9.04 a.m. and 9.08 a.m., but at 9.10 the recording was essentially normal except for some frontal slowing at 5–7 per second. At 9.17 she was wide awake and had a well-maintained alpha rhythm. At 9.28 she was still awake but the amplitude of the alpha rhythm and other waves was dropping slightly. Some drowsiness appeared with hyperventilation. At 9.37 a.m. glucose was given I.V. and at 9.40 a.m. her previous intermittent, excessive drowsiness had reappeared.

Clinically she felt less drowsy at the lower blood-glucose levels.

*Comments.* This patient showed a definite diminution of drowsiness under hypoglycaemia and an abrupt return of drowsiness following glucose. The diminution in drowsiness appeared to run roughly parallel to the blood-glucose levels.

*Case 2.* Male, aged 36 years, with narcolepsy and cataplexy.

The pre-insulin EEG showed no abnormality apart from some drowsiness. As the blood glucose dropped from 93 mg. per cent. to 39 mg. per cent. little or no drowsiness was observed. At 9.30 a.m. the blood glucose was 39 mg. per cent. At this time generalized theta activity along with some generalized delta activity appeared from all leads. At 9.48 a.m. I.V. glucose was given and at 9.50 a.m. drowsy patterns again appeared along with normal brain activity. Drowsiness at this time was so marked that the drowsy patterns appeared almost immediately upon closing of the eyes.

Clinically he was less drowsy at the lower blood-glucose levels.

*Comments.* This patient also, like Case 1, showed a diminution of drowsiness under hypoglycaemia and an abrupt return of drowsiness following glucose. It has since been discovered that this patient was inadvertently given methamphetamine hydrochloride 5 mg. at 7 a.m. Despite this the changes are striking.

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*Case 3.* Male, aged 22 years, with narcolepsy and vivid, disturbing dreams.

The pre-insulin EEG showed a stable recording with considerable excessive, intermittent drowsiness and slight frontal slowing. After injection of 23 units soluble insulin at 8.48 a.m. the blood glucose fell to its lowest level of 30 mg. per cent. at 9.10 a.m. At this time frontal slowing was still present but had not increased. Drowsy activity had decreased considerably. At 9.13 a.m. generalized slowing from all leads was noted in the form of 6–7 per second activity. At 9.20 a.m. blood glucose was 36 mg. per cent. and the patient complained of some sleepiness and palpitation. At 9.30 a.m. blood glucose was 72 mg. per cent. and the generalized slowing had decreased. Glucose was then given intravenously following which drowsiness was noted to appear much more readily.

Clinically the changes were not striking until glucose was given when he felt much more sleepy.

*Comments.* This case was less impressive than Cases 1 or 2 but nevertheless there was considerable reduction in drowsiness on the EEG at the lower blood-glucose levels and drowsiness was noted to be increased after intravenous glucose was given.

*Case 4.* Male, aged 40 years, with narcolepsy, cataplexy, and vivid, disturbing dreams.

During the pre-insulin part of the recording the patient had great difficulty in staying awake. The fasting blood glucose was 99 mg. per cent. and at 8.50 a.m. 25 units of soluble insulin was given intravenously. No change appeared in the EEG until the blood glucose dropped to 43 mg. per cent. At this time generalized slowing maximal in the frontal regions appeared. A considerable amount of drowsy activity was present then but as the blood glucose dropped to 27 mg. per cent. very little drowsy activity was noted. At 9.42 a.m. I.V. glucose was given and the recording at 9.45 a.m. again showed excessive drowsiness.

Clinically the patient reported feeling less drowsy at the lower blood-glucose levels.

*Comments.* This recording follows the general pattern of the others although the diminution in drowsiness under hypoglycaemia is less striking than Cases 1 and 2.

*Case 5.* Male, aged 31 years, with narcolepsy, cataplexy, sleep paralysis and sleep hallucinosis.

As in the previous cases the only pre-insulin EEG change shown was excessive drowsiness reappearing within seconds after the patient had been roused. The fasting blood glucose was 94 mg. per cent. At 8.50 a.m. 26 units soluble insulin was injected intravenously. At 9.03 a.m. the recording showed almost no drowsy activity; the blood glucose was then 70 mg. per cent. At 9.10 a.m. the blood glucose was 49 mg. per cent. and the recording showed no drowsiness. At this time, however, background activity showed some instability and occasionally theta activity at 7 per second in short bursts was observed. A few minutes later more generalized slowing with fairly consistent theta activity was noted. At 9.36 blood glucose had risen to 58 mg. per cent. and the background activity was becoming more stable. There was still no drowsy activity. At 9.46 a.m. glucose was given I.V. and by 9.50 a.m. drowsiness was again being observed. This increased throughout the subsequent recording.

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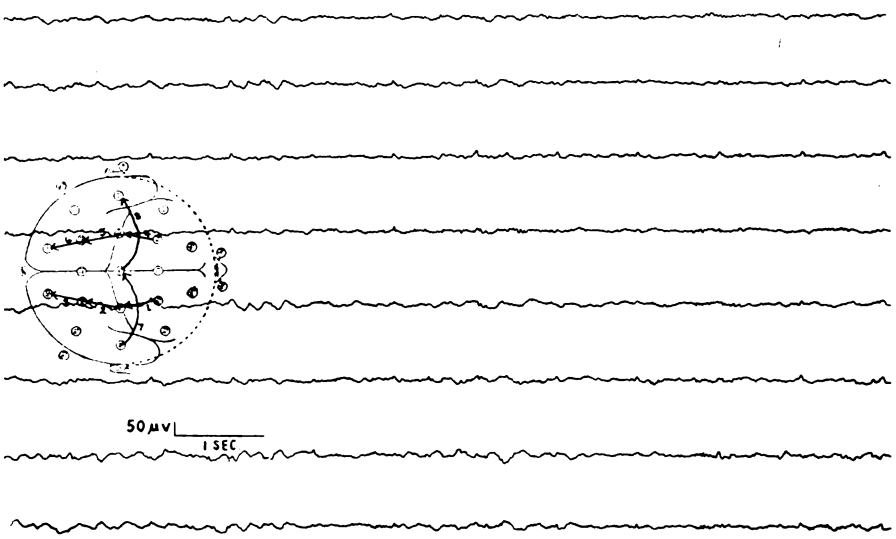



FIG. 1.—EEG of Case 5 prior to insulin injection. Leads as shown. The blood glucose level is 94 mg. per cent. There is much drowsiness.

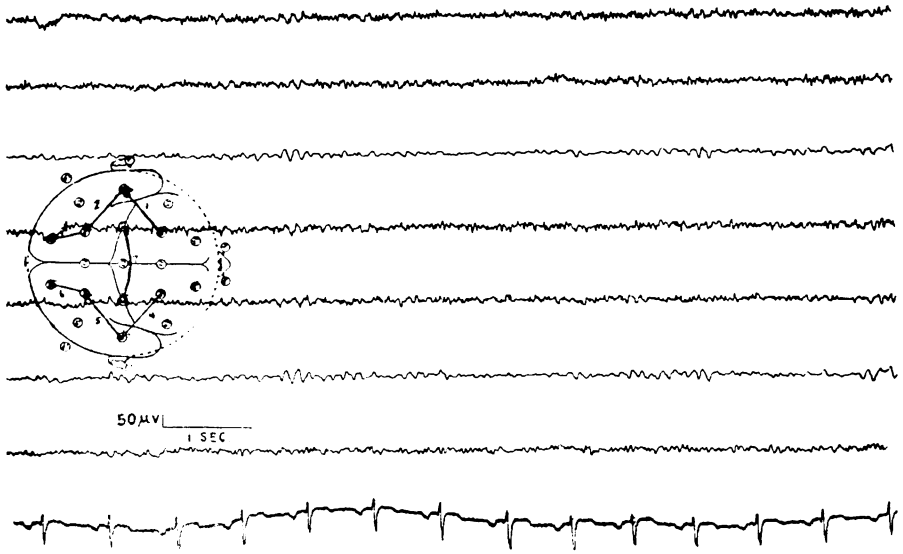



FIG. 2.—EEG of Case 5 twenty minutes after 26 units soluble insulin was injected intravenously. Time 9.10 a.m. Blood glucose 49 mg. per cent. There is no drowsiness. E.K.G. lead III is also shown.

Clinically the patient felt less sleepy after the insulin injection and became more so following the glucose injection.

*Comments.* This man showed little or no drowsiness on the EEG after the insulin was given until hypoglycaemia was terminated by glucose when his previous drowsiness rapidly returned. Samples of the recording are shown in Figures 1–6.

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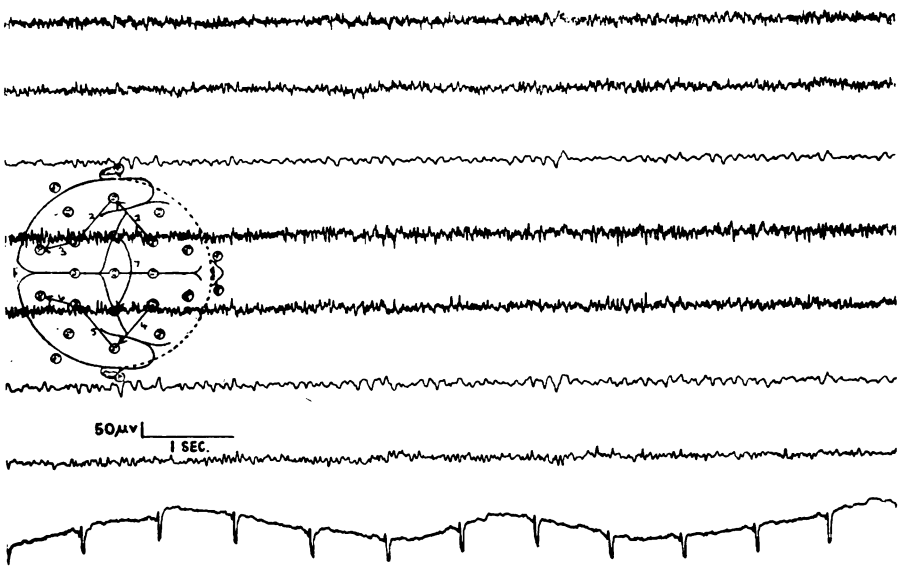



FIG. 3.—EEG of Case 5 at 9.23 a.m. Blood glucose is now 40 mg. per cent. There is no drowsiness.

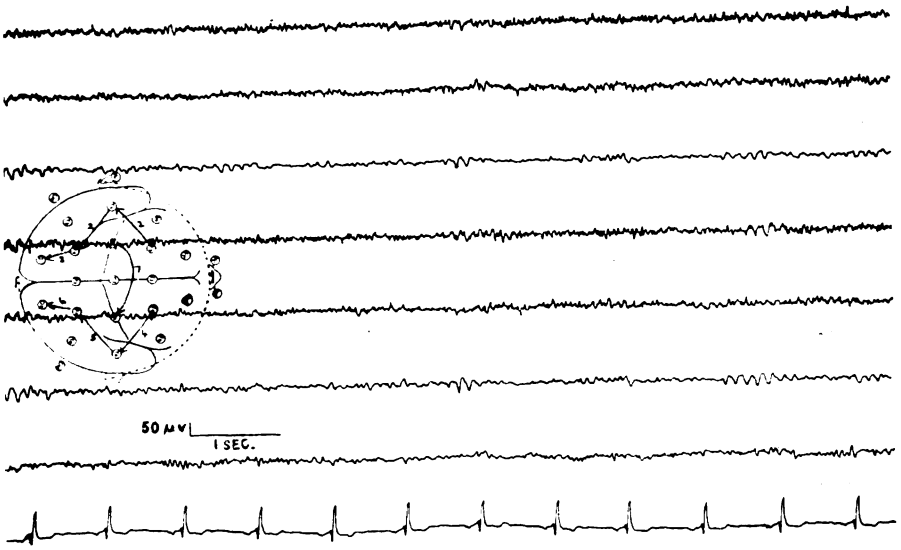



FIG. 4.—EEG of Case 5 at 9.36 a.m. Blood glucose 58 mg. per cent. There is still no drowsiness.

## DISCUSSION

The first question which arises in connection with these findings is: are they non-specific, e.g. were the factors of interest and boredom on the frequent taking of blood samples alone responsible for the changes? Against this the following considerations may be urged.

1. An EEG sleep study was carried out on each case after the technique described by Hoffer (8) and Szatmari and Schneider (15). This involved three

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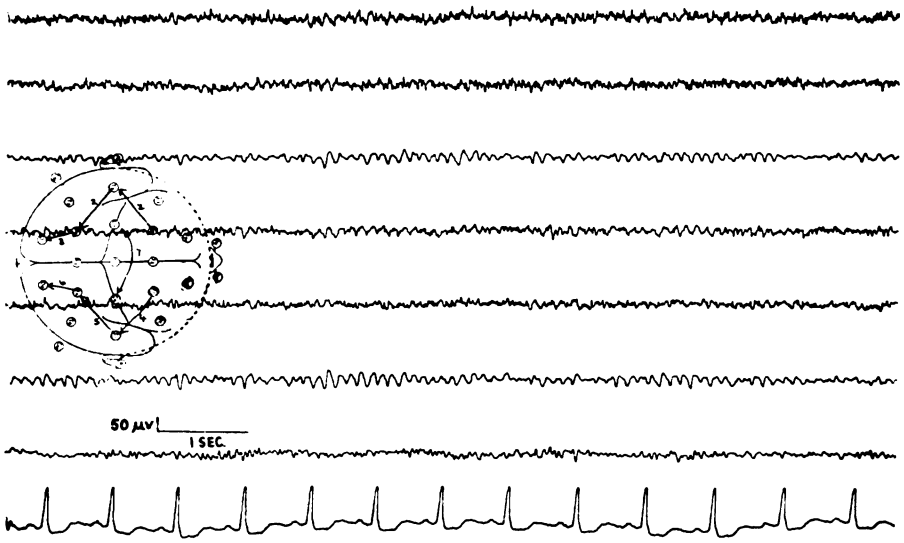



FIG. 5.—EEG of Case 5 one minute after I.V. glucose has been given. Drowsiness has not returned.

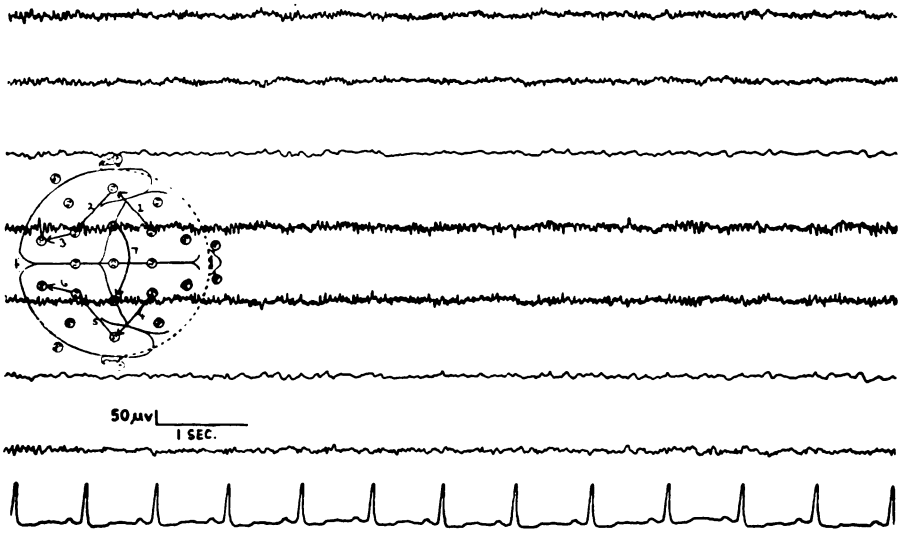



FIG. 6.—EEG of Case 5 six minutes after glucose injection. Some drowsiness is again being observed.

injections: 3 mg. atropine I.M. followed in thirty minutes by 2 mg. physostigmine* I.M. and in a further fifteen minutes by 200 mg. acetylcholine I.V. These injections, though disagreeable, produced very little alteration in the amount of drowsiness present.

* In the published reports of these workers prostigmine was used; later physostigmine was substituted as it had fewer side effects.

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2. The drowsy patterns were removed only very temporarily by other interruptions, e.g. talking, etc., in fact for little longer than the actual stimulus lasted.

3. The diminished drowsiness was most pronounced at lower levels of hypoglycaemia.

4. Sleepiness reappeared very rapidly when I.V. glucose was given.

5. Clinically four of the patients noted some diminution of drowsiness under hypoglycaemia; this is the opposite effect to that which might ordinarily be expected.

6. Suggestion was carefully avoided; in fact the results in the first two cases took us entirely by surprise.

There is, then, some reason to believe that the effect was a specific one. It is possible that it may have been due to central liberation of adrenaline with stimulation of the reticular activating system. This explanation would certainly fit in well with the facts that:

(*a*) Hypoglycaemia is well known to produce increased output of adrenaline.

(*b*) The reticular activating system is adrenaline-sensitive (10, 11).

(*c*) The sympathomimetic amines are effective in narcolepsy.

(*d*) There is a good deal of evidence suggesting a dysfunction of the reticular activating system in narcolepsy (3, 13, 14).

It is interesting to recall in this connection that Weitzner (16, 17) used insulin hypoglycaemia as a treatment in one case of narcolepsy and one of sleep paralysis and claimed to have obtained encouraging results. Weitzner believed that the beneficial change may have been due to an action on the sleep regulating centres in the hypothalamus.

If the findings prove to be peculiar to narcolepsy then they will be of considerable interest since, apart from the EEG changes (excessive drowsiness), there has been a remarkable paucity of constant specific findings in narcolepsy (13). In these five patients the only other laboratory findings of note were some mild disturbances of the Exton-Rose glucose tolerance test in Cases 1–4 (see Table I). Clinically, four of the patients were overweight but otherwise there was no abnormality.

TABLE I

*Results of Exton-Rose Glucose Tolerance Test on Five Narcoleptics*
(Folin-Wu Method; Normal Fasting Glucose 80–120 mg. per cent.)

| Blood Glucose (mg. per cent.) | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 |
|---|---|---|---|---|---|
| Fasting level followed by 50 g. glucose orally | 156 | 97 | 90 | 104 | 103 |
| ½ hour level followed by 2nd 50 g. glucose orally | 133 | 134 | 119 | 128 | 159 |
| 1 hour .. .. .. .. .. .. | 82 | 172 | 160 | 183 | 143 |
| 3 hours .. .. .. .. .. .. | 116 | 113 | 126 | 87 | 79 |
| 5 hours .. .. .. .. .. .. | 113 | 62 | 84 | 98 | 94 |

SUMMARY

The relationship between hypoglycaemia and narcolepsy is briefly discussed. It is pointed out that subjective complaints of "drowsiness" in hypoglycaemic patients are, in many cases at least, not accompanied by drowsy patterns on the EEG.

The EEG changes under hypoglycaemia of five typical narcoleptic patients are then described. All five patients showed diminution of drowsiness in the EEG at low blood-glucose levels and a prompt return of drowsiness following administration of 50 c.c. of 33⅓ per cent.

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glucose intravenously. It is argued that this effect was probably a specific one and that it may have been due to liberation of adrenaline with stimulation of the reticular activating system.

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