OBSERVATIONS IN HYPOGLYCAEMIA. II. BLOOD SUGAR AND CONSCIOUSNESS.

By W. MAYER-GROSS, M.D., L.R.C.P.Ed., and F. BERLINER, M.D.

From the Department of Clinical Research, Crichton Royal, Dumfries.

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SINCE Sakel's introduction of hypoglycaemia into the therapy of psychoses, discrepancies between the level of the patient's blood sugar and the severity of disturbance of consciousness have frequently been noted. The blood sugar decreases in a relatively steep curve within the first and second hour after the injection of insulin ; but only after it has remained on a low level—differing from case to case—for a considerable time does the patient go into coma.

It seems useful to define the clinical signs of coma if it is intended to correlate it with laboratory findings. It is a state of unconsciousness in which the patient cannot be roused by sensory stimuli ; in coma such stimuli do not provoke local and purposeful, but global movements only, if any. Once in coma the patient remains so, independently of the blood-sugar level, which can rise and fall within a certain range without visible change in the clinical picture ; it may even rise to a level at which the patient was awake or could be easily wakened before he went into coma. Subcutaneous or intravenous injections of adrenalin in coma produce a rise in blood sugar without clinical effect. On the other hand, the flooding of the blood stream with sugar by nasal tube feed of a concentrated sugar solution or by intravenous injection of 33 per cent. glucose solution terminates coma and restores consciousness within a few minutes. The latter's action is so immediate that it is considered a practical rule not to stop injecting glucose until the patient is really awake.

From these observations coma appears to be a kind of trigger mechanism comparable to instinctive reactions, such as thirst, hunger or sexual desire. Once established it can only be reversed by specific means.

If this is so, one would scarcely expect the patient to go through the gradual changes of diminishing consciousness which actually happen as a rule. A sudden switch-over from quiet sleep to coma is very rare. The precomatose symptoms of progressive clouding of consciousness can roughly be described as follows : The patient sleeps quietly and relaxed for approximately one hour

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after insulin injection. He then becomes restless and tense, is less relaxed, but remains drowsy for another hour during which he is easily roused by any kind of stimulus; if awakened he answers and converses freely, but easily slips back into drowsiness. One step further, awakening and speaking are impossible, but the patient still reacts with local defensive movements where he is touched, or with grunting noises or opening of his eyes if called by his name. This stage, conveniently called "sopor," may last for an hour or longer, with or without concomitant hyperkinesis; spontaneous waking up with restoration of consciousness and speech for a short period is frequent in this and the precedent stage until coma ensues.

Individual differences in the sequence of disappearing "cognitive conscious functions" (Cohen) can be neglected in this study. Its problem is the relation between state of consciousness and blood-sugar level. Are the precomatose stages similarly independent of the blood-sugar level as is coma? To put the question differently: Is the well known normal response of the blood-sugar level to sensory or emotional stimuli present in the precomatose stage, and has it any influence on the degree of unconsciousness in patients before they go into coma?

The frequent periods of waking up during the second and third hours of the treatment seem to provide ample opportunity for testing this correlation, but there are difficulties of method.

Method.

To establish the basic blood-sugar level of the drowsy patient, it was necessary to take a preliminary specimen without waking him up by the pin-prick and the collection of the capillary blood from the ear lobe or finger. He then either woke spontaneously or had to be roused by a stronger stimulus. Systematic timing of the tests, e.g. every ten minutes, was useless, and many other attempts were of no avail because the patient either woke up when the first specimen was taken, or he was already too deeply clouded to be affected by the following stimulation. If the latter occurred, the tests were used as controls. Eventually we found a small number of patients who remained long enough in a suitable stage, drowsy but easily wakened, both conditions clearly distinguishable by clinical observation. After one or two blood specimens had been taken, the patient either woke up spontaneously or was wakened by sensory stimuli, e.g. lifting his eyelids, slapping his cheeks, tickling his soles, calling his name, etc. When he was able to answer, further specimens were collected, and others when he became more drowsy again.

In another group of experiments the patient was awakened by injecting adrenalin either intravenously (1 c.c. of 1/10,000 solution*) or subcutaneously (0·5 c.c. of 1/1,000 solution*). This method was more reliable and satisfactory

* Sol. Adrenalin Chloride, Parke, Davis & Co.

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because of the longer period and greater degree of wakefulness produced by adrenalin in suitable cases which were in some instances the same as used in the first experiments. There was no difference in effect between slow intravenous and subcutaneous application of the drug. We preferred the latter way of injecting as it is less of a sensory stimulus in itself.

The method of Hagedorn and Jensen was used for the blood-sugar estimations. Only changes of 5 mgm. per cent. or more were regarded as significant.

Results.

(a) *Spontaneous Waking Up or Waking Up by Sensory Stimulus.*

This experiment was successful on ten occasions in four patients. Nine times the waking up of the patient was accompanied by a rise of blood-sugar level of between 5 and 16 mgm. per cent., that is, between 16 and 33 per cent. of the basic level; in one case no change of blood sugar was present, although the patient was awake and answered.

Example of spontaneous waking up.

Miss C. F. R—. 21.xi.39.		Blood sugar, mgm. per cent.
7.26 a.m. :	100 units insulin.	
9.50 a.m. :	Twitching of face; inaccessible; no response if spoken to.	
9.55 a.m. :	1st specimen; struggles against pinprick; calls out. Afterwards quiet; awake; answers; twitching ceases	34
10.03 a.m. :	2nd specimen; does not resist; talks reasonably. After a few minutes twitching starts again; seems more drowsy; restless; becomes more unconscious	50
10.18 a.m. :	Struggles when 3rd specimen is taken	32
10.30 a.m. :	Again quieter and more awake, but does not answer .	38

Example of awakening by strong stimuli.

Miss V. M. T—. 12.xi.40.		Blood sugar, mgm. per cent.
7.20 a.m. :	60 units insulin.	
9.40 a.m. :	Twitching of face; drowsy; not answering.	
9.45 a.m. :	No reaction to pinprick of finger during taking of 1st specimen. *Waking up of patient by tickling of soles.* Patient answers slowly but rationally. Twitching of face is still present	26
9.52 a.m. :	Awake during taking of 2nd specimen. Remained awake	38
10.18 a.m. :	3rd specimen; little reaction to pinprick, but talking rationally	36

(b) *Waking Up by Injection of Adrenalin.*

We succeeded in waking up five patients, two of whom were also subjects in the former experiments, sixteen times by injection of adrenalin. On fourteen

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occasions waking up was accompanied by a rise in blood sugar of between 5 and 15 mgm. per cent., i.e. 17 and 39 per cent. of the basic value.

Two examples of awakening by adrenaline.

D. H. H—. 28.ix.39.	Blood sugar, mgm. per cent.
7.25 a.m. : 75 units insulin. Fasting	84
9.13 a.m. : First slight twitching of face followed by quiet stage.	
9.50 a.m. : Twitching started more violently.	
9.55 a.m. : Twitching of face increased ; pouting	35
10.10 a.m. : Calling out during pinprick	38
10.17 a.m. : *Adrenalin intravenously ;* slow injection, lasting two minutes.	
10.20 a.m. : Twitching ceased.	
10.21 a.m. : Answers questions, seems drowsy, like drunken ; apperception slow ; grimacing	46
10.30 a.m. : Asleep, but follows with his eyes when opened.	
10.31 a.m. :	38
10.40 a.m. : Twitching restarted.	
10.41 a.m. :	37
10.51 a.m. :	38
11.01 a.m. :	35

W. E. W. S—. 19.i.40.	Blood sugar, mgm. per cent.
7.27 a.m. : 110 units insulin.	
9.55 a.m. : Pouting ; twitching ; restless ; grunting ; snoring. Not waking up during taking of specimen	23
10.00 a.m. : Slapping face does not wake him up, nor calling his name ; pouting ; rolling head.	
10.03 a.m. : *Adrenalin intravenously ;* injection lasting one minute.	
10.10 a.m. : Awake ; follows requests ; shows his tongue ; " I am sorry." Still pouting ; more quiet ; slightly roused	38
10.20 a.m. : Goes deeper again ; increasing restlessness	28

In the following example adrenalin injection leads to awakening of the patient, who remains awake, and corresponding blood-sugar tests remain on the higher level.

Miss V. M. T—. 28.xi.40.	Blood sugar, mgm. per cent.
7.38 a.m. : 60 units insulin.	
9.41 a.m. : No reaction to prick ; opens eyes ; no answer	24
9.44 a.m. : Pouting ; twitching of face ; perspiration. *Adrenalin subcutaneously ;* sighs when pricked in arm ; pouting. Face twitches if touched ; perspiration.	
9.51 a.m. : Opens eyes ; conversation about last night's dance. Spontaneous question about treatment.	
9.54 a.m. : Awake	30
10.09 a.m. : Still awake ; pouting starts again ; twitching of mouth during speaking ; reasonable and coherent answers	27
10.19 a.m. : Speaks during taking of specimen ; answers questions ; grimacing during speaking	30
10.35 a.m. : Still awake, as before. Remained awake, no coma ; no sopor.	

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In two experiments the waking up after adrenalin injection was not accompanied by a rise of blood-sugar level. The following is one of these cases:

A. M. A—. 1.x.40.	Blood-sugar, mgm. per cent.
7.15 a.m.: 90 units insulin.	
9.45 a.m.: Shows tongue when asked; resistive during taking of specimen; perseverating on single word if questioned. Becomes more restless; inaccessible; forced grasping; throws head and body about; twitching of face; no answer	38
9.55 a.m.: *Adrenalin intravenously*; slow injection, one minute.	
10.00 a.m.: Answers; speaks naturally about yesterday; some difficulty in finding words. Twitching of face continues.	
10.07 a.m.: Lies in quiet bed; slight twitching of face; talking and complaining during taking of specimen. . .	38
10.10 a.m.: Still answers; little twitching; not fully awake, but accessible.	
10.30 a.m.: Very restless; sopor.	
10.37 a.m.:	38

(c) *Controls.*

Experiments in which the patient did not wake up in spite of strong stimuli were used as controls. In all instances (ten) no rise of blood sugar was found. It was necessary, of course, to make sure that the patient was not already in coma when the second and third specimens were taken.

Summing up, the results of the reported experiments are highly suggestive that the fluctuations of consciousness during the precomatose stage of hypoglycaemia are correlated with variations in the blood-sugar level.

Considering the various factors influencing the blood-sugar level and the difficulty of taking the specimens at the right moment, a certain number of negative results was only to be expected.

Discussion.

It has already been mentioned that because of the technical difficulties a few subjects only were used in our experiments. Nevertheless, it seems justified to apply the results to all fluctuations of consciousness which are so common an occurrence in the precomatose stage of hypoglycaemia.

The interest taken by the psychiatrist in this stage is partially due to the observation frequently reported, and confirmed in a number of our own cases, that a marked improvement in the psychotic condition sets in before the patient has had any coma, i.e. during the first and second weeks of treatment when testing for the insulin dose necessary for the production of coma. Even if the patients go into a daily coma, many pass each time through the changing stages outlined before. The patient wakes up, becomes unconscious again to the accompaniment of vivid vaso-vegetative reactions, and this may

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repeat itself several times. One is often impressed by the quick and relatively complete recovery of those cases which during the precomatose condition exhibit the more dramatic symptoms.

These symptoms are generally related to the counter-action of the adrenal medulla against the insulin effect, first observed by Cannon in cats. Heilbrunn and Liebert (1939), using Trendelenburg's method, found fluctuations of adrenalin content of the blood during hypoglycaemia in man. The amount of adrenalin was dependent on the clinical picture, lowest in deep coma, highest in hyperkinetic cases and in those with marked "self-regulation," i.e. fluctuating between waking and drowsiness. Although transient adrenaemia can account for vaso-vegetative symptoms and their fluctuations, it cannot produce the neurological and mental changes except by simultaneous blood-sugar fluctuations influencing cerebral metabolism. The prompt waking up after adrenalin injection in our second series of experiments makes it probable that the sensory stimulation in our first series acts also via the adreno-sympathetic mechanism.

There are, on the other hand, many reports of fruitless attempts to correlate clinical symptoms with the blood-sugar level. To mention only a few: Horanyi-Hechst and collaborators (1937) found no relation between the blood-sugar curve and the clinical course of hypoglycaemia. Himwich and his collaborators (1939), combining studies in brain metabolism with electro-encephalograms in hypoglycaemia, found oxygen intake a much better indicator of clinical and electric variations than blood sugar. Their work, however, does not deal in detail with the stage of the adreno-sympathetic counteraction. M. Jones (1939), who tried to correlate the changes in pulse rate and blood pressure with the blood-sugar level, had no consistent results. Lately Fortuyn (1941) has again emphasized that the fluctuations of hypoglycaemic symptoms are not explained by the biochemical changes of the blood. He has tried to overcome the difficulties of interpretation by postulating a "diencephalic mechanism" producing all hypoglycaemic symptoms. From analogous, experimental and clinical observations he infers that stimulation of the diencephalon results in fluctuating reactions of a mixed sympatho-parasympathetic type. His theory is of special interest if one thinks of the diencephalon as the possible seat of a trigger mechanism releasing coma.

Even if coma is released on some lower level of integration, the result of our experiments suggests that the precomatose clouding of consciousness and its fluctuations depend on the changing flow of glucose to the part of the central nervous system which is generally regarded as the part most vulnerable to disturbances of metabolism, viz. the cortex. Thus the idea of a double integration of consciousness, diencephalic, disturbed in coma, and cortical, impaired during the precomatose stage, presents itself as a working hypothesis. It certainly would remove some of the discrepancies mentioned at the beginning of this paper.

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The greater sensitivity of the cortex to hypoglycaemia could account for the precomatose disturbances of consciousness and its progressive clouding, whereas the release of coma would be the response of a more resistive subcortical centre. When coma is established, even considerable counteraction of the adreno-sympathetic system remains ineffective ; blood sugar and state of consciousness, so closely correlated during the precomatose stage, seem to be relatively independent one from another. The sharp rise of the blood-sugar level after administration of glucose probably overcomes the disintegration on both levels at once, thus leading to a quick and complete waking up. There are obvious parallels of this hypothesis with well-known theories of normal sleep (see, e.g., Globus, 1940).

Summary.

Once hypoglycaemic coma is established, fluctuations of the blood-sugar level seem to have no influence on the clinical picture, especially on the degree of unconsciousness. During the precomatose stage, however, fluctuations of consciousness are correlated to the blood-sugar fluctuations. This was shown in experiments in which the patient was awakened from a moderately deep drowsiness either by strong sensory stimulation or by injection of adrenalin The therapeutic importance of the precomatose stage, the findings of other workers and their possible explanation is discussed. Some of the difficulties in explaining the mechanism of hypoglycaemic symptoms could be overcome by a hypothesis suggesting that the disturbances of consciousness in the precomatose stage and in coma are related to two different levels of cerebral integration, viz. cortical in the precomatose stage and diencephalic in coma.

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