OBSERVATIONS IN HYPOGLYCÆMIA: IV. BODY TEMPERATURE AND COMA.

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Whereas fall of body temperature is always a danger signal in ordinary starvation and only occurs just before the end, in hypoglycaemia changes of temperature take place in an early stage parallel with the characteristic neuropsychiatric signs. Many workers (Sakel, Gellhorn, Fortuyn and others) have observed and commented on the drop of temperature in coma. The present paper is an attempt to describe the fluctuations of temperature during insulin treatment of psychoses and their correlation with the clinical signs of hypoglycaemia and to discuss their significance.

Material and Method.

The rectal temperature was recorded in eleven male patients on 129 days by means of a thermocouple connected with an electric indicating thermometer (Gen. Electr. X-Ray Corporation, Chicago, Illinois). It is graduated in $\frac{2}{10}$ degree Fahrenheit, but readings to $\frac{1}{10}$ can easily be made. The findings were recorded on a temperature chart every five minutes—an interval which makes ample allowance for the slowness of the instrument.

In the majority of cases the thermocouple was put into position at the time of the first clinical manifestations of hypoglycaemia, i.e. about two hours after injection of insulin. It remained in the rectum for approximately two hours until the patient had been awakened by nasal feed of dextrose or by intravenous injection of glucose.

The patient received his usual coma dose varying between 40 and 200 units insulin (see Table I); on 20 days lower doses were given in order to observe the effect of hypoglycaemia without coma on temperature; these days also served as controls. On 23 days the thermocouple was inserted before the insulin injection and records were taken over the whole forenoon.

Table I.

Cases.	Duration of illness.	No. of days observed.	No. of coma days.	Coma doses, insulin units.	Temperature °F. Average rise.	Temperature °F. Average fall.
1. Sc—	2½ years	6	2	130	0·5	0·9
2. Bo—	3 months	13	13	160	0·4	0·7
3. Th—	1 year	30	27	150	0·8	0·6
4. To—	2 weeks	3	2	60	0·4	0·5
5. Ro—	2 years	14	12	70	0·5	0·7
6. Gu—	2 ,,	13	13	40	0·4	0·7
7. Sh—	4 ,,	11	8	80	0·3	0·7
8. Va—	3 ,,	2	0	200	0·2	..
9. Kn—	11 months	3	3	80	0·7	1·0
10. Ke—	6 years	3	3	150	0·3	0·5
11. Ha—	4 ,,	31	26	90	0·3	4·3

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It was possible to record the temperature during the various clinical manifestations of hypoglycaemia, including moderate motor excitation and, on a few occasions, epileptiform convulsions. Only in severe general restlessness of choreatic or similar character could the thermocouple not be kept in position.

Nine patients were schizophrenics of different types, early cases as well as cases of long standing; one was diagnosed chronic mania and one psychopathic personality, both with schizoid features.

The room temperature in the centrally heated insulin ward was controlled hourly; it varied between 58° and 68° F., being lowest in the morning at the time of the insulin injection and highest at about 11 a.m., when the patients were in coma.

Results.

The general trend of the temperature curve can be described as follows: It remains level for two hours after the insulin injection; it begins to rise when the first hypoglycaemic symptoms appear, perspiration, flushing, oral movements, restlessness, increase in muscle tonus and drowsiness. After half to one hour the curve turns and begins to fall, while the symptoms become more marked and others, like rhythmic movements of head and limbs, general spasms, forced grasping, make their appearance together with the deeper clouding of consciousness. The

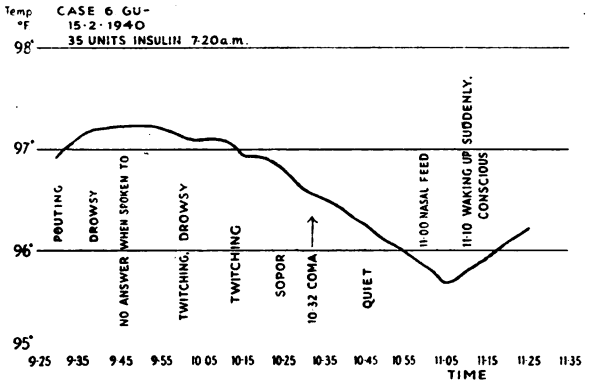


Fig. 1.—Typical curve.

temperature sinks below the starting level. Clinical signs of coma appear during the decline. The latter continues until the coma is interrupted by dispensing sugar. While the patient regains consciousness, the temperature rises, slowly returning to the original level. On days without coma there is sometimes the initial rise, but, as a rule, no fall of temperature.

The number of observations diverging from this course was small. Rise before coma was absent on eleven days; six times coma was diagnosed without corresponding fall of temperature. Fall without coma was only seen on three occasions, all in the same patient (Case 11), whose excessive reactions make a separate discussion necessary.

The amount of temperature changes differed considerably between different patients (Table I), but its scatter in the same patient on different days was very small. The daily repeated pattern of clinical symptoms characteristic for the special case corresponded to equally constant temperature readings. A somewhat higher scatter found in Case 3 was accompanied by greater variations of the clinical picture. No correlation could be established between the coma doses of insulin and the amount of temperature changes (Table I).

From a more detailed analysis of the curves the following points are of interest: the drop of temperature observed by Fortuyn within the first hour after the insulin injection was present in 11 out of 23 days on which the early stage was recorded; it exceeded 0·2° F. only in case Ha—, whose temperature fluctuations were excessive at all stages.

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Profuse perspiration was present during the precomatose rise as well as during the subsequent fall of temperature and further outbursts appeared in coma. It subsided after sugar administration when the temperature rose again. This was the only phase in which shivering, which is uncommon in hypoglycaemia, was observed.

On some occasions the greatest restlessness coincided with the maximum of

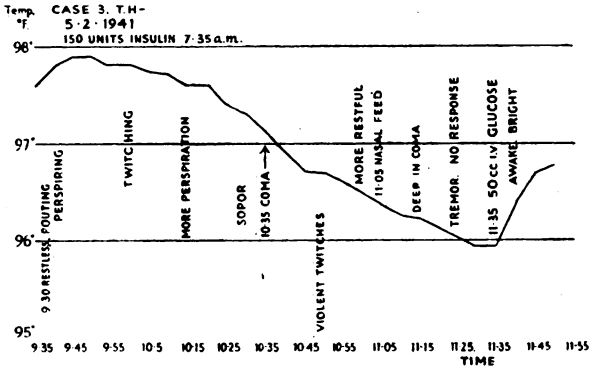


FIG. 2.—Delayed waking-up after nasal feed; waking-up by intravenous glucose.

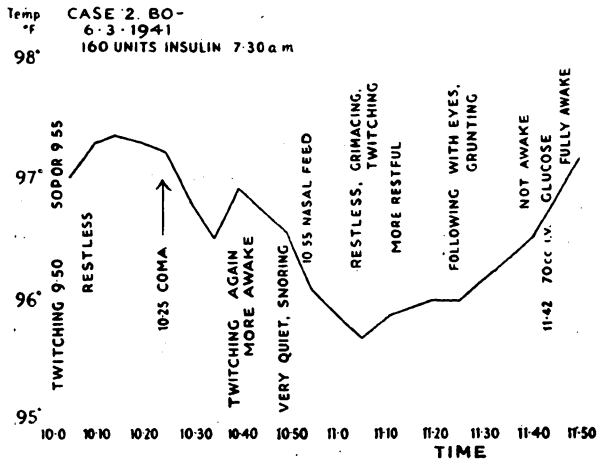


FIG. 3.—Rise of temperature during period of increased restlessness in coma.

temperature rise, but generally twitching and other forms of hyperkinesis increased even more during the decline of the curve, and especially the spastic condition of muscles seemed independent of the temperature. Sometimes it was plausible to correlate delay in temperature fall or transient rises with more violent movements, especially if the patient became more awake through the movements (Fig. 3). On the other hand the deep and constant fall of temperature in patient Ha— (Case 11, fig. 6) was not correlated to his motor signs.

There were individual differences in the relation between coma onset and temperature. In patents 2 and 4 coma started almost simultaneously with the turning of the curve towards decline, while in Case 11 the temperature fell for 60 to 90 minutes before coma started. In the other patients the time was between 15 and 30 minutes.

The fall continued as long as the patient was in coma, and it is difficult to say how long it would have fallen had the coma been extended over more than the usual hour. In Case 11 the temperature fell once from 98·4° to 92°

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without alarming clinical signs or sequelae. If after nasal feed the coma became deeper, as it sometimes does through the output of the patient's own insulin, the

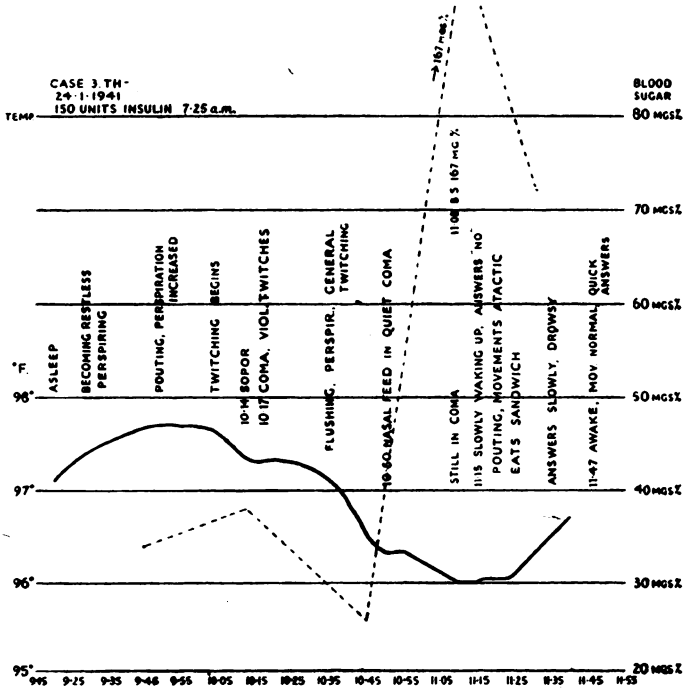


FIG. 4.—Temperature ————. Blood sugar - - - - - - -.

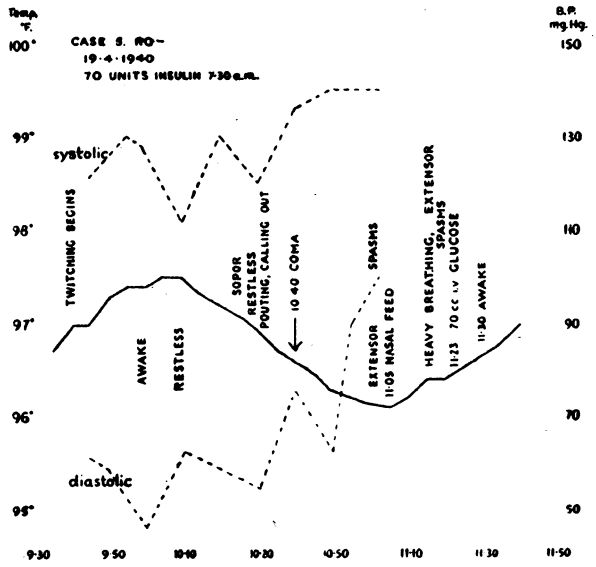


FIG. 5.—Temperature ————. Blood pressure - - - - - - -.

curve, which seemed to flatten out first, declined again (Figs. 2 and 4). Intravenous glucose given until the patient was conscious always produced an immediate rise of temperature.

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Synchronism of temperature rise and return of consciousness was complete; only on a few occasions was there a delay, but never exceeding ten minutes. The temperature thus provides an objective indicator of the end of coma, while there seems no clear relation to the beginning of coma. One has, however, to remember that waking up is much more easily observed clinically than the transition from sopor to coma.

The return to the normal temperature level was not instantaneous although the rate of rise was generally quicker than that of fall. Where there was a considerable falling off, it often took an hour before the original level was regained.

Simultaneous control of blood-sugar level and temperature showed that the rise of blood sugar was not so closely correlated to the upward turn of the temperature curve as was the return of consciousness. In spite of high blood-sugar findings after nasal feed, the temperature remained low until the patient awoke (see Fig. 4).

Adrenaline given subcutaneously or intravenously only influenced the temperature if the patient was awakened by the injection.

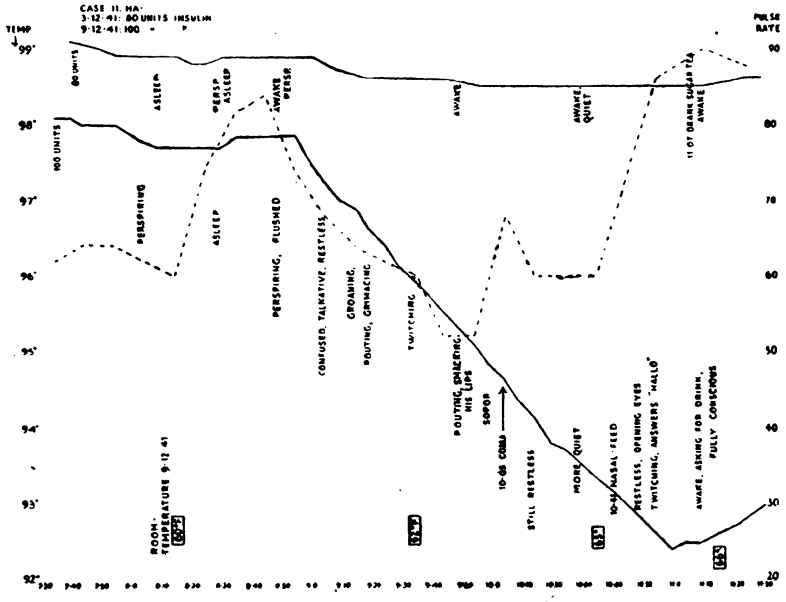


FIG. 6.—Temperatures ———— on a day without coma and on a coma day in the same patient. Pulse rate - - - - - - - - of the coma day.

The pulse rate (taken every ten minutes) followed the changes in temperature, quickening with the precomatose rise and slowing down with the decline to the neighbourhood of 50. In coma it fluctuated irregularly (Fig. 6). The changes in blood pressure (high pulse pressure in precomatose stage with leaping fluctuations, lowering and becoming steadier during coma) seemed not more closely correlated to the temperature than the other clinical signs (Fig. 5).

The temperature during three epileptiform seizures due to hypoglycaemia observed in the same patient showed a small but definite rise immediately after the fit when the patient was more awake. On one occasion the temperature also went up before the fit, corresponding to violent, preconvulsive twitchings.

DISCUSSION.

a. *Peripheral Explanation of Temperature Rise.*

There are two possible peripheral explanations of the precomatose rise of temperature, (1) muscular exertion, and (2) adrenaemia; no corresponding explanation of the subsequent fall, however, can be offered.

1. The temperature began to rise when after two hours of quiet, relaxed sleep the patient showed signs of increasing motor activity and of growing muscular

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tonus. The individual degree and character of the restlessness varies considerably, but muscular rigidity was always present and advanced with the rising temperature.

Quantitative recording of our patients' movements was not available; it seems doubtful if it would have been of much use if the muscular tone had not been recorded as well, because of the frequent spastic conditions during rest. We had to rely on clinical impressions. From these one could, for instance, relate the greater average rise of temperature in patients 3 and 9 to their marked restlessness before coma; but it was not certain if their restlessness exceeded that of patients 6 and 7, whose temperature rose only half the amount. To surmise similar correlations between the average fall of temperature in coma and the amount of restlessness during this period proved impossible. On single days, however, a relatively small fall could be plausibly related to greater restlessness during coma. In general, movements increased and extended over larger parts of the body for some time after the decline of temperature had begun. Even after the onset of coma, many patients continued moving and twitching, and in those who became quieter the muscles remained spastic. Rest with complete relaxation in coma was seen only for short periods. All one can say is that it is possible that the precomatose temperature rise was caused by motor symptoms.

2. Secretion of adrenaline into the blood stream, during the exposure of an animal to cold, is known to stimulate heat production, being the first and finest protective mechanism against cold. Similarly the output of adrenaline which counteracts insulin during the precomatose stage may contribute to the increase of temperature at this stage. From the observations of Heilbrunn and Liebert (1939), it seems that the adrenaline content of the blood goes parallel with the motor signs; thus both factors seem to co-operate in producing the precomatose rise of temperature. Like the motor symptoms, however, signs of adrenaemia (flushing, circum-oral pallor, bounding pulse, etc.) remain present and often become more marked during the subsequent fall of temperature; they are seen in coma without apparent influence on the temperature curve.

b. *Temperature Fall and Problems of Localization.*

For an explanation of the temperature fall in hypoglycaemia it seems necessary to resort to some central disturbance. Considering the numerous controversies concerning the central representation of metabolic functions, one can expect neither a clear-cut localization nor a comprehensive theory at the present time.

The cortex is the first to be affected by hypoglycaemia, but while the cortex takes part in the mechanism of heat regulation in animals (Pinkston, 1934; Kennard, 1935), there is no proof that depression of the cortex in man has any influence on rectal temperature, and clinical evidence is to the contrary. On the other hand, there is general agreement that the hypothalamus is the centre of heat regulation.

The prominence of symptoms referable to the autonomic nervous system in hypoglycaemia suggests that the chief autonomic centres in the hypothalamus are directly affected. That the hypothalamus is affected in hypoglycaemia has been explained from its role in regulating carbohydrate metabolism. This hypothalamic function is, however, still very much under debate (Long, 1940). Recent systematic studies on autonomic symptoms in hypoglycaemia, e.g. of pupils, pulse rate and blood pressure (Parker, 1940), of dermographia, gastric secretion, leucocytosis (Fortuyn, 1941) have confirmed the clinical impression that both sympathetic and parasympathetic functions are active above their normal level in all stages of hypoglycaemia. There is some difficulty in explaining this constant hyperactivity. Fortuyn compares it with the attacks of "autonomic epilepsy" observed by Penfield (1929) and McLean (1934) in cases of tumour in the third ventricle pressing upon the hypothalamic region. Hoagland *et al.* (1939), from their observations in hypoglycaemic dogs, favour an explanation from the reduction of cortical control; but none of the well-known clinical examples of cortical impairment seems to be accompanied by similar autonomic signs—a fact which makes the study of hypoglycaemia symptoms all the more important.

Parker thinks that he can differentiate three distinct stages of autonomic reaction to hypoglycaemia; one of parasympathetic predominance during the first two hours after insulin injection, followed by a period of predominantly

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sympathetic tone lasting one hour and corresponding to the precomatose restlessness, and finally parasympathetic predominance again during coma. Leaving out the first stage for the present, these observations seem to provide sufficient explanation for the temperature changes described above if they are due to hypothalamic stimulation. The posterior hypothalamus contains, according to Fulton, chiefly sympathetic representation and is also the seat of the centre of heat production; the middle and anterior nuclei are predominantly parasympathetic and the centre for heat loss is located anteriorly. The problem remains how to account for the shifting of stimulation, from the posterior to the anterior hypothalamic nuclei. Besides, even Parker—who himself avoids details of localization—emphasizes repeatedly that in all three of his stages symptoms of a heightened excitability of both divisions of the autonomic systems are present. If that is so, one should expect irregularities and fluctuations of temperature readings and not the constant pattern found in our observations.

To arrive at a more satisfactory hypothesis, one has to supplement localization of the autonomic functions by their teleological interpretation; it is generally agreed that stimulation of the posterior hypothalamus mobilizes the body's carbohydrate reserve through the sympathetico-adrenal mechanism. This reaction takes place after insulin injection with the presumed purpose of combating the parasympathetic effect of insulin. The struggle between these antagonistic functions is most lively in the precomatose phase, but continues during coma, where there is still sympathetic counteraction as described above. That eventually the sympathetic counteraction is outbalanced and that, at the same time, heat production —localized in the same region—fails, may be due not to a breakdown of the heat centre, but to the exhaustion of the body's carbohydrate reserve, the main source from which metabolic activity could be sustained on an elevated level. The reserve has run out, used up by the precomatose hyperkinesis.

Such a theory would render unnecessary the postulation of successive stimulation of different hypothalamic centres and would explain most of the autonomic symptoms in coma, including temperature fall. It would almost make it possible to forego any reference to a centrally disturbed regulation.

The simultaneity, however, of the fall of temperature with the onset of coma and of its end with the temperature rise points again to a hypothalamic site where both functions can be deranged. In fact, damage to the posterior nuclei, in animal experiments or from a tumour in man, is followed by hypothermia and abnormal somnolence (Davison, 1940). It therefore seems justifiable to consider the posterior hypothalamus as the diencephalic region where coma is released, as postulated in a former paper from very different reasons (Mayer-Gross and Berliner, 1941).

c. *Temperature Changes in Sleep and Coma.*

Can the temperature fall in normal sleep throw any light on our observations? The problem has recently been thoroughly re-investigated by Kleitmann and his collaborators (1939). He found the downward trend of temperature at night which is part of the diurnal temperature rhythm accentuated by the onset of sleep. Awakening, however, was not characteristically followed by a change of body temperature. On the other hand lying down, without sleep, after standing for some time, invariably led to a fall of temperature, and the opposite was true if the procedure was reversed. Consequently, although he recognizes what he calls the "wakefulness centre" in the hypothalamus and its proximity to the body-temperature centre, Kleitmann is convinced that the temperature variations are not primarily of central origin, but dependent upon the variations in muscle tonus. "At any time of the day and night it is possible to lower the temperature, compared to normal, by relaxing the body musculature and to raise the temperature by increasing muscle tonus." Conditions of muscles in hypoglycaemia being as described, it is obvious that Kleitmann's explanation is not applicable to coma, which in itself, of course, is not identical with sleep, even if it should be released from the same diencephalic focus.

Nearest to sleep was the state of our patients during the first two hours after receiving insulin, and it is in accordance with the prevalence of parasympathetic functions during sleep, as established by Hess (1925), that Parker found parasympathetic predominance during this first stage of hypoglycaemia.

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Further observations of Kleitmann's relevant to our problems are the marked individual differences of temperature fall among his subjects. He found such differences if they merely assumed the horizontal position, as well as in sleep, there being a definite personal character of shape and level of the temperature curve. The adaptability of the diurnal temperature fluctuations to changed conditions, e.g. to night work, also varied considerably with different persons. This inequality of the individual responsiveness of the heat-regulation mechanism, peripheral or central as it may be, could account for the different averages of hypothermia in our patients. It seems doubtful, however, if the excessive reaction in our patient Ha—, whose temperature fell seven times lower than the average of the others, can also be attributed to an individual variation within the normal.

d. *Temperature in Schizophrenia.*

Views on primary disturbances of the autonomic nervous system in schizophrenia being as controversial as they are, any discussion on the relation between Ha—'s hypothermic reaction and his schizophrenic illness must be very speculative. Especially about heat regulation, opinions are widely divergent. In contrast to some investigators (Gottlieb and Linder, 1935; Finkelmann and Stephens, 1936) who found a failing heat regulation in schizophrenics, Jung and Carmichael (1939), examining catatonic stupors, were unable to discover any abnormality of peripheral or central heat regulation. Gjessing, in his intensive research on bodily functions in periodic catatonics (1932–39), found only small variations, of 1° C. or less, in the average temperature level corresponding to the patient's mental state; none of his cases showed excessive thermolability. Rectal temperatures of schizophrenics studied under varying environmental conditions by Freeman (1939) did not differ from normal controls. All the same, the tendency to consider schizophrenia as a " deficiency in some central autonomic co-ordinating process " (Grinker, 1939) attracts hypothetical thinkers; its counterpart is the rationale of insulin and convulsion treatments, according to which their results are achieved through stimulation of the autonomic centres which have been slackened by some noxious factor of unknown nature (Gellhorn, 1938). Whatever the value of this and other theories, there can be little doubt that the autonomic nervous system is stimulated through hypoglycaemia as borne out by our temperature observations.

We conclude this discussion with the history of and some notes on patient Ha—, who showed such an extraordinary hypothermia, although he seems otherwise a very ordinary case of long standing, catatonic schizophrenia.

CASE 11.—Ha—, born 1916. Normal child, healthy, cheerful, sociable; good scholar, fond of sports, excellent athlete. Insidious beginning of illness at 18, when a medical student. Depressed, listless, unable to concentrate. Ideas of reference, people reading his thoughts, making sounds and signs referring to his wickedness. December, 1935, admitted to hospital. Delusional, hallucinated, inadequate emotional expression, apathetic. April, 1937, transferred to Crichton Royal. Behaviour erratic; outburst of violence. Lacking initiative; sleep disturbed. Uncontrolled laughter, restless, refused to occupy himself. March, 1938, after 15 convulsions produced by cardiazol marked improvement, regained liveliness, active in sports and gymnastics. Well behaved when on holiday with parents. August, 1938, discharged.

Accompanied his father to India, worked in a garage for some time; his interest soon died down. On homeward journey friendly and sociable. Returned to hospital May, 1939, after speaking of an uncontrollable desire to kill somebody. On readmission much the same as before treatment; apathetic, unable to finish a sentence, hallucinated, giggling, inclined to impulsive attacks. Physically in very good condition. October, 1939, to March, 1940, insulin treatment; 56 comas, 7 fits. Lively immediately after waking up from coma. Improved slowly, but without regaining spontaneity. For a short time bright and talkative, took part in sports and games, wrote letters. Relapsed in May, 1940. Unresponsive, stiff and completely passive. Since deteriorated, more catatonic attitudes, repeating the same word over and over. For short periods violent and agitated. December, 1941, to January, 1942, second course of insulin treatment without effect.

Morning and evening temperatures fluctuated within normal range during insulin treatments. As in other cases, evening temperatures between 98·5° and 99° F. occurred on some coma days, but not regularly. On several occasions we tried to stop the fall of temperature in coma by drying the patient's skin, dressing him in fresh pyjamas, and applying hot water bottles—without success. Attempts to quicken the return to the normal temperature level by making the awakened patient stand in an upright position were equally unsuccessful.

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SUMMARY.

Systematic observations of rectal temperature in 11 patients undergoing insulin treatment showed a small rise of temperature during the precomatose period followed by a fall, which continued into coma until its interruption by dispensing carbohydrate. The temperature rise after the fall coincided with the return of consciousness, thus providing an objective indicator of the end of coma.

The extent of temperature changes differed between different patients, each patient having an individual pattern corresponding to his clinical symptoms during hypoglycaemia.

The relation of the temperature curve to blood sugar, pulse rate, blood pressure and injection of adrenaline are described.

Whereas the precomatose temperature rise can be explained by the patients' motor behaviour and the adreno-sympathetic counter-action, the fall in the coma stage is probably due to a central disturbance. The problem of its localization and of that of the concomitant autonomic symptoms is discussed. A hypothesis is offered covering the total of autonomic symptoms in hypoglycaemic coma.

The possible relations of our findings to recent observations of temperature in sleep and to the schizophrenic illness of our subjects are examined.

We wish to thank Dr. P. K. McCowan, the Physician Superintendent of the Crichton Royal, for his interest in our work and for his permission to publish these observations. Our thanks are also due to the staff of the Insulin Department for their willing collaboration, especially to Miss C. M. Baker, our Insulin Sister.

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