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Part I.—Original Articles.

POST-HYPOGLYCAEMIC ENCEPHALOPATHY IN SAKEL'S INSULIN TREATMENT.

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INTRODUCED in 1933, Sakel's pharmacological shock treatment [Sakel (1935*a*, 1935*b*, 1938)] is now regarded as a valuable method of treatment in schizophrenia. The complications which may ensue during the treatment are, however, both numerous and dangerous, and may be classified according to the system predominantly affected as follows:

(1) The Respiratory System.
(2) The Cardiovascular System.
(3) The Nervous System.

Complications of the respiratory and cardiovascular systems are comparatively rare, acute pulmonary oedema being the most serious complication affecting the respiratory system, while acute myocardial failure is a rare fatal complication of the cardiovascular system. Complications of the nervous system, on the other hand, are frequent and, ranging as they do from mild conditions such as transitory aphasia to fatal prolonged coma, constitute the major hazards of the treatment.

A. NEUROLOGICAL COMPLICATIONS OF SAKEL'S TREATMENT.

While the condition known as prolonged coma is the commonest and most fully reported complication, a large number of other complications occur which indicate that damage to the central nervous system may vary from the slightest degree to the most profound. These complications may be classified according to the main presenting symptoms as follows:

(1) *Confusion.*—Slight degrees of confusion persisting for a few hours after interruption of the coma are common in practice and references to the condition are fairly frequent, e.g. Gillman and Parfitt (1938), Katzenelbogen *et al.* (1939), Coyne (1940), Kant (1940). Gillman and Parfitt (1938) mention

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that " we have given intravenous sugar more than 300 times to patients who were not sufficiently conscious 30 minutes after the feed, usually with satisfactory results, but fairly frequently a certain amount of confusion, mild headache and malaise persists." These authors' comment on such cases is especially noteworthy—" great care should be ensured in such cases when deciding the duration of the next shock, for we believe such conditions are often forerunners of delayed recovery of a serious kind."

(2) *Stupor.*—This may be present either alone or with one or more of the neurological abnormalities described below. In cases of the former type, the patient may be able to obey simple passive commands and the swallowing reflex is present. In practice, patients are frequently stuporose for short periods after the hypoglycaemia has been terminated, but Scherb and Stone (1938) mention a case in which the patient was stuporose for 8 hours, while a patient of Kant (1940) was " in a deeply clouded, stuporose condition " for 10 hours.

(3) *Aphasia.*—A number of cases have been reported in which aphasia occurred, usually of a transient character and clearing up after a few hours. Sometimes the aphasia occurs alone [Ruslander (1937–38), Goldman (1940), Golden (1937)] but it is usually accompanied by other abnormal nervous signs and symptoms. Schatner and O'Neill (1938) report the occurrence in a male patient of a paralysis of the right arm, which disappeared in 20 minutes, being accompanied by a motor aphasia which persisted for about an hour, while a female patient developed paralysis of the right arm and right leg, persisting for 3 hours and accompanied by a motor and sensory aphasia which cleared up in 1½ hours. Scherb and Stone (1938) record a case which had a transient aphasia accompanied by a severe headache, while Wortis, Bowman *et al.* (1937) noted three instances of transitory aphasia associated with facial weakness. A right hemiplegia and aphasia persisting for 10 hours in a patient aged 58 years is mentioned by Bond, Hughes and Flaherty (1939). Kant (1940) records that in a case of motor and sensory aphasia occurring on the 52nd day of treatment, the sensory features of the aphasia disappeared before the motor ones.

(4) *Dysarthria.*—A mild transient degree of dysarthria is frequently found in patients recovering from coma which has been interrupted by stomach tube, but Horwitz, Blalock and Harris (1938) record a case of an 8-year-old boy who was still stuporose 10 hours after intravenous injection of glucose. At 11 hours he was able to say Mama, but otherwise his speech was dysarthric.

(5) *Echolalia and Echopraxia.*—Horwitz, Blalock and Harris (1938) mention a case of post-hypoglycaemic stupor in which " as his physical condition improved and his speech returned, marked echolalia and echopraxia were observed."

(6) *Rotary movements.*—Read, Heilbrunn and Liebert (1939) record a case in which " we observed some peculiar rotary movements setting in 1 hour after interruption of shock. These movements lasted about 2 hours, and could be started in either direction by a slight push to the shoulder."

(7) *Diplopia.*—Schatner and O'Neill (1938) record three instances of diplopia in two female patients, who complained of double vision after interruption of hypoglycaemia and disappearing after about 20 minutes.

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(8) *Facial paralysis.*—In addition to the facial paralysis occurring as part of a hemiplegia, Binzley and Anderson (1938) mention a case in which marked motor activity occurred during administration of glucose by vein, there being a shifting Babinski response and a paralysis of the right facial muscles.

(9) *Hemiplegias.*—Several instances of this complication are reported in addition to those mentioned under (3) above. The condition is usually transitory, clearing up after a few hours [Wortis, Bowman *et al.* (1937), Young *et al.* (1937), Golden (1937), Horwitz, Blalock and Harris (1938), Binzley and Anderson (1938), Bond, Hughes and Flaherty (1939), Schatner and O'Neill (1938)]. Read, Heilbrunn and Liebert (1939) cite a case in which a female patient developed a permanent left Hoffman sign, slight left facial palsy and increased reflexes. Palisa (1938) found among 170 cases, 6 patients who developed a right-sided hemiplegia, 1 with a left-sided hemiplegia, and 1 patient who showed an alternating right and left hemiplegia on no fewer than 5 occasions during a course of 55 shocks. The higher incidence of right-sided hemiplegias may be due to the greater development of the left cerebral hemisphere in right-handed people, rendering it more vulnerable to the adverse effects of insulin.

(10) *Epileptiform seizures.*—The term "convulsion" appears to be used loosely in the literature to cover both the generalized myotonic spasms, which may last up to 10 minutes, and the typical epileptiform seizure similar to that seen in idiopathic epilepsy. Read, Heilbrunn and Liebert (1939) state that 34 patients developed a convulsion at some time during the treatment. Three of these developed epileptic states, the first immediately, the second within 4 hours, and the third 15 hours after interruption of shock, but no details are given as to the exact nature of the convulsions, or whether they occurred while the patient was mentally clear or still in post-hypoglycaemic stupor. Similar accounts of convulsions are given by Scherb and Stone (1938), Young *et al.* (1937), Katzenelbogen (1939), Morrow (1938), Katzenelbogen *et al.* (1939), Kant (1940), Gillies (1937) and Gillman and Parfitt (1938), but in all these cases even where an epileptic fit is mentioned specifically it is difficult to be sure that intense generalized tonic spasms are not referred to. Typical major epileptiform seizures certainly occur, usually during the *early* stages of shock, sometimes before the patient has become unconscious, the effect frequently being that the unconscious patient spontaneously awakes owing to the rise in blood sugar following the seizure, but it is very difficult to see how such a seizure can occur in the absence of symptoms once the hypoglycaemia has been effectively interrupted, unless the patient develops "after shock" with its consequent fall in the blood sugar. Gillman and Parfitt (1938), however, report the case of a female patient who had a series of 15 fits at 10-minute intervals approximately 26 hours after interruption, during which time "she remained well."

The remaining complication of the nervous system is post-hypoglycaemic coma. It appears that the nervous complications cannot be divided into definite categories, but that they shade gradually from the mildest degree of mental clouding, through severe degrees, of such clouding, transient aphasias and paralyses, epileptiform convulsions and so on to the fully developed

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post-hypoglycaemic coma, which, it will be seen, can itself be of varying degrees of severity, lasting from a few hours to several days. We turn now to a consideration of this condition.

B. POST-HYPOGLYCAEMIC COMA.

I. Synonyms.

Prolonged coma ; non-hypoglycaemic coma ; protracted shock.

II. Definition.

Post-hypoglycaemic coma [Goldman (1940)] occurs when the patient does not recover consciousness after sufficient glucose has been given either orally or intravenously ordinarily to terminate the coma. The condition is marked by varying degrees of hyperthermia ; hyperventilation, both hyper- and tachypnoea ; motor excitement, rigidity and tonic-spasms ; the Babinski response may or may not be present, but the corneal reflex can usually be elicited. The condition may persist for from a few hours to several days, and may result in (*a*) complete recovery, (*b*) recovery with varying degrees of cerebral damage, or (*c*) death (*Brit. Med. J.*, 1940).

III. Reported Cases.

De Morsier and Mozer (1936) first described the condition of post-hypoglycaemic coma in a morphine addict who was being treated with insulin. The first case occurring in Sakel's treatment was reported in the following year by Salm (1937). Following this a large number of reports have appeared. The following list is comprehensive except for articles in a few foreign journals which were not available for this study : Franke (1937), Gillies (1937), Kobler (1938), Leppien and Peters (1937), Molony and Honan (1937), Rossman and Cline (1937–38), Sherril and McKay (1937), Wortis, Bowman *et al.* (1937), Baker (1938), Binzley and Anderson (1938), Cammermeyer (1938), Doring (1938), Easton (1938), Finiefs (1938*a*), Gillman and Parfitt (1938), Horwitz *et al.* (1938), James, Freudenberg and Cannon (1938), Kastein (1938*a*, 1938*b*, 1938*c*), Lazell (1938), Lester (1938–39), Morrow (1938), Milch and Bolles (1938), McKendree (1938), Plattner (1938), O'Neill (1938), Scherb and Stone (1938), Telatin (1938), Timmer (1938), Baker (1939), Baganz and Laxon (1938), Braestrup (1939), Freed and Saxe (1939), Katzenelbogen (1939), MacKeith and Meyer (1939), Murphy (1939), Ribeiro and di Lascio (1939), Skaug and Hellem (1939), Theato (1939), Wortis and Lambert (1939), Yahn and da Silva (1939), Coyne (1940), Goldman (1940), Jansen and Waaler (1940), Kant (1940), Klein and Ligterink (1940), Vie and Opolon (1940), Polatin, Strauss and Altman (1940), Robinson and Robinson (1940), Abely and Feuillet (1941), Cleckley and Templeton (1941), Gralnick (1941), Abely and Feuillet (1942), Lawrence, Meyer and Nevin (1942), Proctor and Easton (1942), Schou (1942), Rivers and Rome (1944), Wechsler (1944).

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IV. Modifications of Sakel's Hypoglycaemic Treatment.

It has been generally assumed that prolonged coma is caused by the induction of coma of such *depth* that irreversible changes have occurred in the brain. Unfortunately, the whole question of coma is confused in the literature owing to the differing standards of coma adopted by various authors and the frequent absence in published papers of the standard adopted by the writers. The present writer (Spencer, 1947) has reviewed the question, showing that Sakel himself used the term to cover all stages of unconsciousness from "sopor" (von Angyal, 1937) to unconsciousness and complete areflexia. The position would have been clarified considerably if a common standard of coma such as that adopted by Wilson (1937) of unconsciousness with Babinski responses and absent corneal reflexes had been generally agreed upon. Insufficient attention has also been paid to the influence of the *time* for which patients have been allowed to remain in coma, and the question has not been investigated as to whether prolonged coma is more likely to follow a deep coma lasting for a short time or a light coma induced for a longer period.

Owing to the dangers inherent in coma of Wilson's standard, medical and nursing staff shortages, etc., there has been a tendency in recent years for only the lighter types of unconsciousness to be induced, [e.g. Sherman, Mergener and Low (1941), Sandison and McGregor (1942)], although the duration of the hypoglycaemia remains about 5 hours. Early in 1945 a modified form of insulin therapy was instituted at the Joint Counties Mental Hospital, Carmarthen, as shortage of staff did not permit the practice of "deep-coma" therapy, and as events proved, this modified therapy cast considerable light upon the importance of the *duration* of unconsciousness in the production of prolonged coma.

Under this modified form of insulin treatment, the patients were given just sufficient insulin to induce unconsciousness after the lapse of some 3–4 hours from the time of the injection. This corresponds to the state called "sopor" by some authors. Frequently, but not invariably, the plantar responses become extensor during the period of unconsciousness, but the corneal reflexes are always briskly present. It will thus be seen that the depth of the coma is very light, and in no way comparable with the deep coma normally induced, in which the plantar responses are always extensor and the corneal reflexes either very sluggish or completely abolished. It was found, however, that once the "sopor" dose of insulin had been attained, the addition of a further 5 units was usually sufficient to extend the length of "sopor" to periods of from 1–4 hours, after which the patient spontaneously awoke. A total of 8 or 9 hours' hypoglycaemia might thus be induced, including 1–5 hours of light unconsciousness. *Duration of "sopor" replaced depth of coma as the object of the treatment.* Profuse perspiration might occur, but the sopor is never deep enough for tonic muscular spasms to be produced. Patients usually require about 30–40 units to produce sopors of 2–4 hours, but in the 50 patients to whom the treatment has been given, only 3 have required more than 50 units, there being one case requiring 70 units. It will thus be seen that the modified treatment is altogether lighter than Sakel's treatment.

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It is no alternative to the latter treatment, and was only instituted because shortage of nursing and medical staff did not permit the giving of Sakel's treatment, and following the good results achieved by some workers with ambulatory insulin treatment [Polatin and Spotnitz (1942 and 1943).] While the results of the treatment do not compare with those obtained by Sakel, they are good enough to warrant its continuation until it can be replaced by the more thorough-going technique.

Despite the very light state of unconsciousness induced in this modified treatment, two of the first 30 patients treated developed prolonged comas, one of which terminated fatally. Case-reports of the two instances of prolonged comas will now be given, as they illustrate several features not mentioned previously in the literature.

V. Case Reports.

Case 1.—Female, aged 54 years.

Diagnosis.—Involutional melancholia.

The patient's illness dated from January, 1938. On 28.vi.38 she was admitted to the Maudsley Hospital. She showed the usual characteristics of involutional melancholia, intense depression, morbid feelings of guilt and unworthiness with somatic delusions, such as that she was suffering from venereal disease, and that consequently her bowels were stopped up. Prior to admission she had attempted suicide. She became more depressed during the following year, and was transferred to the City of London Mental Hospital on 29.vi.39. She remained unimproved, and was discharged to her husband's care on 7.x.39. A feature was noted at this time which became more marked later on. This was the conscious wish of the patient not to recover. She refused to co-operate in her treatment because she wished to die and not get well.

On 11.iii.41 she was admitted to the Joint Counties Mental Hospital, Carmarthen, her condition being as outlined above. Strong death wishes were prominent, and she stated that she could not and did not wish to recover. Electrical convulsive therapy was tried without effect. When the modified insulin treatment was instituted in the Hospital early in 1945, the patient was started on a course of treatment despite the length of her illness. On 12.iii.45 she was given an initial dose of 10 units. This was increased by 5 units each day, until she went into sopor 4½ hours after the injection of 35 units. During the following weeks the dose varied between 20–30 units, sopor usually lasting about 3–4 hours. She always awoke spontaneously, and at no time did her condition give rise to any anxiety. Her mental state gradually began to improve, inasmuch as her depression became less profound, but throughout she constantly expressed her wish to die and not to get better. Treatment was continued for 4 months and unexpectedly terminated as follows:

6.vi.45: Dose of insulin—20 units—sopor 4 hours. Spontaneous awakening. Took tea and supper and appeared her usual self.

7.vi.45: Dose of insulin—25 units—sopor 6 hours. She came round spontaneously, sufficiently to take a cup of tea, but was very confused, and almost immediately relapsed into a stuporose state in which she could be spoon-fed with fluids, but in which she was not conscious and was unable to speak. As this state showed signs of continuing, she was regarded as being in post-hypoglycaemic coma. Adequate fluids, intravenous glucose, sodium chloride, vitamins B and C were given in order to maintain her general condition, which was very good. Lumbar puncture was performed, but the fluid did not appear to be under increased pressure and its biochemical analysis gave normal results. Temperature 98·2° F., pulse 96, respirations 24.

8.vi.45: Her condition is unchanged except that at the end of the day her temperature has risen to 101·8° F. and her pulse, of good volume, is 118/minute. Respirations, 20/minute. Fluids have been continued and she takes well by spoon-feeding, being able to swallow easily. Her eyes are open, and one has the impression that she is just beyond being fully conscious. One feels that if she made

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the effort she could become fully conscious, but her attitude is one of complete apathy and she is incontinent of urine. She remains mute. Her condition is most interesting and unusual. It appears as though she is deliberately willing herself to remain out of contact with reality, a condition in keeping with her frequently expressed wish to die.

9.vi.45: Her condition remains unchanged. Treatment as before. General condition good. She continues to give the impression that she is deliberately refusing to regain full consciousness. She sits propped up in bed looking vacantly in front of her in a completely passive attitude. Temperature 102° F., pulse 110/minute, respirations 18/minute.

10.vi.45: During the day her general condition has deteriorated considerably. She remains just "around the corner" from full consciousness, but her physical condition is causing concern. She has been given continuous "drip" saline to maintain the circulation and has had a transfusion of one pint of blood. Late in the day she became cyanosed, but this was relieved by oxygen given through a nasal catheter. Temperature 103° F., pulse 120, respirations 24.

11.vi.45: Her heart failed finally at 1.0 a.m. Permission for a post-mortem examination was refused.

Comment on Case.

This case is interesting for two reasons:

(1) It proves conclusively that depth of coma is not necessarily the most important factor in the production of post-hypoglycaemic coma, but that the duration of hypoglycaemia may be of even greater importance. This patient's hypoglycaemic state was so light that she did not even develop extensor plantar responses, yet despite this, after a period of 6 hours' unconsciousness at the "sopor" stage she developed prolonged coma. The significance of this will be more fully discussed later.

(2) The psychological factor seemed to enter significantly into the outcome of the coma. This also will be discussed in detail later, but it may be said now that the patient's frequently expressed wish not merely to die (a passive wish), but her wish not to get better (an active wish), indicated such a powerful development of the Freudian death-instincts that she died when she need not have done so. In watching her attitude during her prolonged coma one was almost forced to the conclusion that the patient deliberately willed herself to death.

CASE 2.—Female, aged 24 years.

Diagnosis.—Paranoid schizophrenia.

This patient had been ill for 2 months before her admission to the Joint Counties Mental Hospital, Carmarthen, on 14.xii.45. Several near members of her family were below average in intelligence, but no cases of psychotic breakdown among them could be elicited. The patient had always been of a shy, introverted disposition, and no adequate external cause for her breakdown could be found.

Condition on admission.—During the interview her manner was pleasant and equable, but her answers to questions were frequently delayed owing to blockage of thought. Her level of general intelligence was definitely subnormal. She was unable to do the 100–7 test, she knew the number of pence in 1*s.* 9*d.*, but could not do the 3*d.*'s in 3*s.* 9*d.* and the 2*s.* 6*d.*'s in 15*s.* She had no knowledge of current affairs. She showed marked ideas of reference, and believed that people around her were constantly laughing at her. A number of non-systematized paranoid delusions were easily elicited. She believed that her parents were trying to rob her of some money which she had in the bank, and that her brother-in-law had tried to kill her with a pocket-knife on a number of occasions. She could give no reason for his wanting to do this except that he was against her.

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She believed that her food in the hospital was being poisoned, and that one of the nurses wanted to kill her as she was in league with her parents. She was aurally hallucinated for a man's voice which abused her, but she would not discuss her hallucinations in detail. In view of her persecution at home and her hallucinatory experiences she had decided to commit suicide as soon as possible. There was mild incongruity between her thought processes and mood. She completely lacked insight into her mental state and believed that she was perfectly well.

Her physical state was satisfactory except that she had a raised blood pressure (178/94).

During the following 2 weeks she received a course of 7 electrical convulsions, as a result of which she was considerably less restless, although her schizophrenic thought processes remained the same, nor did she develop any insight into her condition. In view of her poor response to E.C.T. a course of modified insulin therapy as given to the previous patient (Case 1) was started on 7.i.46.

Responses to insulin.—The initial dose of insulin was 20 units, increased on succeeding days as follows until she developed sopor: 25, 30, 35, 40, 45, 50, 55, 60, 65, 70. On 70 units she went into sopor for the first time for the unexpectedly long period of 4½ hours, from which she spontaneously awoke. In view of the length of this sopor, the dose was reduced the following day to 60 units. The injection was given at 7.0 a.m. and she went into sopor at 11.10. The sopor was quite light, although Babinski responses were present from 11.30–12 noon. Her condition was perfectly satisfactory and sopor was allowed to continue for 5 hours, i.e. until 4.10 p.m., at which time she was given 100 c.c. of glucose (40 per cent.) intravenously. Her sopor lightened further following this, but she did not regain consciousness. Twenty minutes later she was given a further 100 c.c. of glucose (40 per cent.) intravenously without effect and she was then judged to be in post-hypoglycaemic coma.

Her condition at this time differed remarkably from that seen in most cases of post-hypoglycaemic coma. She appeared to be asleep. Respirations were regular, deep and of average rate. Her pulse was regular, of good volume, although a little fast (90/minute). She did not perspire, and all her reflexes were normal. At no time did she show tonic extensor spasms. *She remained in this condition for 5 days.* Her general condition remained satisfactory throughout this time and never gave rise to any anxiety. Her treatment consisted of generous quantities of milk, water, sodium chloride, halibut oil (for vitamins A and D) and marmite (vitamin B) by stomach tube; ascorbic acid and vitamin B parentally to ensure absorption. Her temperature rose to 99·6° F. on the first day, but became normal on the second day and did not rise again.

At the end of the fifth day of coma she spontaneously awoke. Her speech was slurred for the first few hours and then rapidly improved. By the following day she appeared to be her normal self apart from a slight degree of confusion which persisted for 3 days, when it cleared up.

Condition 7 Days After End of Prolonged Coma.

Her mental condition has improved considerably compared with what it has been on admission. Most noticeably, all her paranoid delusions and hallucinations have disappeared and *she is completely amnesic for ever having held them.* She is considerably more alert and active than on admission, and spontaneously takes part in the ward activities. She is, however, still entirely lacking in insight into her mental state and has no idea why she had to come to the hospital. She is also amnesic for the whole of the period of her prolonged coma.

She remained in this condition until her discharge from hospital 3 months later. A follow-up 4 months after her discharge indicated that her parents considered that she was better than she had been for a number of years, and that she was doing her work on a farm perfectly satisfactorily, although she was still rather shy and reserved.

Comment on Case.

Like the preceding case, this patient illustrates the view that great depth of coma is not necessary for the production of post-hypoglycaemic coma, but that the *duration* of hypoglycaemia is of equal importance. This patient had

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a period of 9 hours' hypoglycaemia, including 5 hours of sopor. Although the sopor was very "light," the hypoglycaemia was sufficiently long to produce irreversible changes in the brain which caused the post-hypoglycaemic coma, which was also of a superficial character.

VI. Aetiology of Post-Hypoglycaemic Coma.

(1) *Incidence of Post-Hypoglycaemic Coma.*

It is difficult to arrive at a satisfactory estimate of the incidence of the complication owing to the large number of unreported cases, and because the percentage incidence is frequently not given in those which are reported. In the present author's series of 146 cases the condition occurred 4 times (2·7 per cent.). Dussik (1936 and 1938) found it occurred 5 times in 5,000 treatments. In a survey of post-hypoglycaemic coma in 20 hospitals in U.S.A., Lester (1938–39) found a total of 25 examples among 1,173 completed insulin cases (2·1 per cent.). Kant (1940) had 9 cases in a series of 61 patients (15 per cent.); Goldman, 23 in a series of 108 patients (21·1 per cent.); Rivers and Rome (1944) 38 in a series of 225 patients (17·1 per cent.); while Schou (1942) found the high proportion of 127 out of 375 patients (30·1 per cent.). There seems to be no satisfactory explanation for these widely differing degrees of incidence.

(2) *Age and Sex of Patients.*

A review of the recorded cases indicates that the ages of the patients vary from 20–48 years, with the age group 20–30 years predominating. As the age of onset of schizophrenia is also chiefly in this age group, no significance would appear to attach to the age of the patient as far as liability to post-hypoglycaemic coma is concerned.

Among a sample of 96 cases in the literature, there were 52 males and 44 females, so that the sexes would appear to be equally subject to the condition.

(3) *Race and Climate.*

Post-hypoglycaemic coma has been reported from all countries where Sakel's treatment has been tried. In America, white and negro patients seem to be equally liable to the condition.

(4) *Type of Schizophrenia in Affected Patients.*

Catatonic, paranoid and hebephrenic types of schizophrenia are all reported, with the paranoid form predominating. The absence of cases of the dementia simplex type is probably due to the fact that these patients tend not to receive insulin treatment in view of the poor results obtained with such patients. Easton (1938) states that he had become increasingly wary of a certain type of patient, tall, asthenic, with cold, blue hands and feet, whom he had found to tolerate insulin very poorly. Lester (1938–39) believes that prolonged coma is due to the fact that a number of patients possess a constitution which is unable to withstand with average impunity a prolonged period of hypoglycaemia. No details are given, however, as to the type of constitution the author refers to.

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That the condition is not restricted to schizophrenia is shown by the present author's case, Case 1, who was an involutional melancholic, while Cleckley and Templeton (1941) had two patients, one with a manic-depressive psychosis and the other with hysteria, who developed post-hypoglycaemic coma.

(5) *Dose of Insulin at which Post-Hypoglycaemic Coma Occurs.*

Analysis of 83 published cases in which is given the dose on which prolonged coma occurred gives the figures of the following table :

TABLE I.

Units of insulin	20–39	40–59	60–79	80–99	100–119	120–139	140–159	160–179
Number of cases	2	12	11	16	10	10	6	4
Units of insulin	**180–199**	**200–219**	**220–239**	**240–259**	**260–279**	**280–299**	**300–324**	**325 +**
Number of cases	2	4	1	1	1	—	1	4

While there may be a slightly greater proportion of cases in the 80–99 units group, in general the range of doses corresponds closely to that used in uncomplicated cases, and undue sensitivity to insulin, requiring the use of smaller doses than usual, does not appear to be of aetiological significance in post-hypoglycaemic coma.

(6) *Number of Daily Treatments after which Post-Hypoglycaemic Coma Occurs.*

In order to ascertain whether prolonged coma is more likely to occur at any stage in the course of the treatment, the 55 cases in the literature which give the necessary information were analysed to find :

(*a*) The day of treatment on which the initial coma occurred.

(*b*) The number of cases preceding the prolonged coma.

(*c*) The total number of treatments preceding the prolonged coma.

The results of the analysis are set out in the following table. To ensure that the table is arithmetically complete, it is necessary to know, in addition to

TABLE II.

(A) = Day of treatment of initial coma.
(B) = Number of comas before prolonged coma.
(C) = Total number of treatments before prolonged coma.

Case Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
(A)	6	6	—	4	2	—	—	9	21	5	4	30	8	5	4	4	—	14	5
(B)	3	5	21	—	3	—	—	6	1	1	2	1	14	1	11	36	35	2	4
(C)	9	11	21	4	5	7	21	25	22	6	31	22	6	25	40	44	16	9	—

Case Number	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37
(A)	—	—	—	9	13	10	6	8	10	13	12	6	14	6	12	5	2	—
(B)	30	16	7	6	12	25	4	9	3	5	23	1	—	28	5	9	7	—
(C)	—	24	20	27	25	35	10	17	13	18	35	7	28	34	17	14	9	55

Case Number	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55
(A)	—	6	—	—	3	3	11	8	6	—	—	5	6	4	3	—	6	—
(B)	—	2	—	—	1	1	6	26	5	—	22	2	5	1	2	—	11	—
(C)	52	8	18	19	14	4	17	34	13	6	41	7	11	5	5	7	17	6

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the above factors, the number of non-coma treatments the patient received after the initial coma, but this information is not given in several of the articles, so that the table is not arithmetically complete.

These results are given in detail above as they show that in a certain proportion of cases there is a definite association between the occurrence of prolonged coma and the induction of coma after only a few days' treatment (Cases 1, 2, 4, 5, 10, 11, 14, 19, 26, 31, 36, 43, 47, 49, 51, 52, 53 and 55). The results may also be grouped as follows:

TABLE III.

Days	1–4	5–9	10–14	15–19	20–24	25–29	30–34	35–39	40+
Number of patients whose *number of days of treatment before initial coma* fall into the opposite groups	11	19	9	—	1	—	1	—	—
Number of patients whose *number of comas preceding the prolonged coma* fall into the opposite groups	18	8	4	1	3	3	1	2	—
Number of patients whose *total number of treatments preceding the prolonged coma* fall into the opposite groups	3	16	6	11	5	3	3	2	5

This table brings out—

(1) That prolonged coma may occur at any time during the course of Sakel's treatment: 10 of 54 patients had received more than 30 treatment-days before their prolonged coma occurred, while 5 had actually received more than 40 daily treatments. Attention may be drawn particularly to these findings. While, as is seen below, the majority of cases of prolonged coma occur through coma being induced too rapidly in the course of treatment, yet a considerable proportion (20 per cent.) of patients go through more than 30 days' treatment normally and then suddenly develop prolonged coma. Constitutionally, they can hardly be different on the day they develop prolonged coma from what they were on the previous 30 days. By the 30th day of treatment the coma dose of insulin is usually standardized, and yet unexpectedly the patients develop post-hypoglycaemic coma. Rivers and Rome (1944) point out that in a large proportion of their 38 patients who developed prolonged coma deeper stupors had previously been observed, and yet the patients had not previously developed prolonged coma. It was the existence of this group of patients which led to the attempt to determine whether the probably shorter-acting intravenous insulin would give rise to fewer neurological complications than the usual subcutaneous or intramuscular insulin (Spencer, 1947).

(2) That, despite the above, the majority of cases of prolonged coma occur in the early days of the course of treatment and especially, as noted above, if coma is induced only a few days after the commencement of the treatment. Eleven of 41 patients had less than 5 treatments before coma was induced, and 30 of 41 patients had less than 10 treatments. In addition, of 40 patients, 18 had received fewer than 5 comas and 26 fewer than 10 comas when they went

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into prolonged coma. Of 41 patients, 3 had received less than 5 treatments in all and 19 less than 10 treatments in all before post-hypoglycaemic coma set in. Since prolonged coma can occur at any time during the course of treatment, other factors must obviously play a part, but the table shows the danger of increasing the dose of insulin so rapidly that coma is reached by the 5th or 10th day. Thirty-nine of 41 patients who developed prolonged coma had coma induced within 15 days of commencing the treatment, and it is probable that had coma been induced over a period of, say, 21 days, the incidence of prolonged coma would have been considerably less, since only 2 of the same 41 patients had had coma induced over periods of larger than 15 days. It is not merely a question of increasing the daily dose of insulin by equally small doses in all cases, as each patient's reaction to insulin is peculiar to that patient, but of determining the daily increase according to the development of the signs of hypoglycaemia in each patient so that coma will be reached by about the 21st day. Because of this, Lester's (1938–39) finding that a series of patients who developed prolonged coma after less than 4 comas had been given a daily increase of 12·5 units, whereas a similar series of patients who developed the condition on, as an average, the 20th coma had been given a daily increase of 10·6 units, is not significant.

VII. Pathology of Post-Hypoglycaemic Coma.

(1) Morbid Anatomy.

In the reports in the literature of post-mortem examinations of patients who have died from post-hypoglycaemic coma, attention has been devoted almost exclusively to the brain, from the pathology of which the various authors have attempted to deduce the cause of the condition. Microscopic studies of other organs have only been reported in a few cases, but as Dunner, Ostertag and Thanhauser (1933), Enstene and Altschule (1931), Ernstene *et al.* (1935), Jorgensen (1940), Tannenberg (1939) and Terron and Malesani (1939) have shown in animal experiments, the heart, skeletal muscles and the liver may also show marked changes, and the cause of prolonged coma may be found in dysfunction of some organ other than the brain, despite the primarily neurological clinical picture seen in the condition. The morbid anatomy may therefore be considered under the various systems and organs which are affected by hyperinsulinism in human subjects:

(*a*) The Central Nervous System.
(*b*) The Cardiovascular System.
(*c*) The Respiratory System.
(*d*) The Liver.
(*e*) The Pancreas.
(*f*) The Suprarenal Glands.
(*g*) The Kidneys.

This will be followed by a review of the results of animal experiments and an examination of the theories as to the cause of prolonged coma which have been advanced as a result of the study of the morbid anatomy.

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(A) *The Central Nervous System.*

As has been mentioned, pathological studies of patients who have died from prolonged coma have been confined mainly to the brain, which has also been closely studied in animals subjected to large doses of insulin. A number of the articles in the literature have been reviewed by Lawrence, Meyer and Nevin (1942), who, however, did not restrict themselves to a consideration of changes found in patients dying in post-hypoglycaemic coma during Sakel's treatment, but included also cases of spontaneous hypoglycaemia due to adenomata of the pancreas, and also diabetics who had developed hypoglycaemia through an overdose of insulin. As the latter patients, especially, were not physically normal at the time when they became hypoglycaemic, as are the patients undergoing Sakel's treatment, reports on their morbid anatomy will not be considered.

The general pathological findings in the central nervous system in the reported cases may be summarized as follows: The neurones may suffer from general or localized ischaemia, which may be so severe that the entire neurones may disappear. The neurones of the frontal, temporal and occipital lobes are more frequently affected than those of other lobes, with the heaviest incidence of damage falling on the Cornu Ammonis and its Sommer sector in ticular. There is a reactive response, either proliferative or degenerative, on the part of the glial elements, while the blood vessels show a proliferative endarteritis, with perivascular exudation, neoformation of blood vessels, pseudocalcification of the media and sometimes thrombosis in the cerebral vessels. These changes will now be considered in detail as they affect the various parts of the brain.

(1) *Meninges.*

The condition of the meninges has not usually been reported on, but Ferraro and Jervis (1939*a* and 1939*b*) noted that in one case they were normal with marked congestion of the meningeal blood vessels, while Gralnick (1941) found the same congestion of the blood vessels in meninges which were transparent to the naked eye.

(2) *External Appearance of the Brain.*

De Morsier and Mozer (1936) found no naked-eye changes in the brain of a morphine addict who had died in prolonged coma following treatment with insulin, as did Ferraro and Jervis (1939*b*) in 4 schizophrenia patients. Similar findings have been reported by Cammermayer (1938), Jacob (1939), Jansen and Waaler (1940) among others. Gralnick (1941), however, found that the brain of a patient dying after 10 days of prolonged coma was oedematous with narrow, shallow sulci.

(3) *Internal Structure of the Brain.*

(a) *Neurones.*—There is a considerable degree of unanimity in the reports of the changes found in the neurones by various authors, although some confusion exists through the use of different stains and a somewhat loose termino-

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logy to describe the changes found. Reports of detailed histological studies of the brain have been published by, *inter alia*, Cammermayer (1938), Doring (1938), de Morsier and Mozer (1936), Ferraro and Jervis (1939*a* and 1939*b*), Gralnick (1941), Jacob (1939), Jansen and Waaler (1940), Kastein (1938*a*, 1938*b*, 1938*c*), Kobler (1938), Leppien and Peters (1937), Lawrence, Meyer and Nevin (1942), Salm (1937), Scherb and Stone (1938), Timmer (1938), and MacKeith and Meyer (1939).

As regards the changes in the individual neurones, these have been found to vary from the slightest to the most profound, from chromatolysis, shrinking, vacuolysis, swelling of the nucleus, eccentric placing of the nucleus, homogeneous cytoplasm, swelling of the Nissl bodies, to complete disappearance of the neurones. On the other hand, the neurones might be shrunken, deeply stained, with irregular nuclei and distorted dendrites, or elongated and triangular with sharp edges, the cytoplasm being homogeneous and eosinophilic, the nucleus eccentric—Spielmeyer's ischaemic degeneration.

The distribution of these changes in the neurones varies according to different authors, although some areas are more frequently reported as being affected than others. Cammermayer (1938) found that the superficial sub-pial layers were the most affected, but that generally the cortical changes had no elective character. Usually, while almost every neurone in the cortex might appear to be more or less affected, the portions of greatest devastation were frequently limited to areas about 1 cm. sq. The frontal, parietal and occipital lobes were more frequently markedly affected than other areas [Cammermayer (1938), Ferraro and Jervis (1939*b*), Gralnick (1941), Leppien and Peters (1937), MacKeith and Meyer (1939), and Salm (1937)], and in particular the Sommer section of Ammon's horn appeared to be unusually vulnerable. As regard the layers of the cortex, the more superficial layers were more affected than the phylogenetically older lower ones. Brodman's third layer seemed to be electively affected in a number of cases, producing an effect of pseudolamination. Cells around the calcarine fissure were particularly well preserved in a case of Doring (1938), which led the author to ascribe a vascular origin to the condition.

In the *basal ganglia* similar changes to those occurring in the cerebral cortex have been described by Cammermayer (1938), Ferraro and Jervis (1939*a* and 1939*b*) and Leppien and Peters (1937). As a rule, however, the changes in the basal ganglia were not as profound as those in the cortex.

In the *midbrain* and *medulla oblongata* some nerve cells are usually affected, but only to a mild degree compared to the changes in the cortex [MacKeith and Meyer (1939)].

In the *cerebellum* Ferraro and Jervis (1939*b*) and Gralnick (1941) found that the Purkinjë cells were deeply involved, numerous cells having completely disappeared. Of those that remained, the nuclei showed marked alterations ranging from chromatolysis to vacuolization and colliquation. Similar lesions were found in the inferior olive. In MacKeith and Meyer's (1939) case, however, the changes in the cerebellum were comparatively slight, the Purkinjë cells being somewhat paler than usual and the lipoid content of the neurones in the olivary body being probably a little increased.

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It appears from the above review that the effects of hyperinsulinism upon the part of the brain depend upon the phylogenetic age of the part. The phylogenetically young portions, especially the highly developed occipital, parietal and frontal lobes appear to be particularly vulnerable. Of the layers of the cerebral cortex, the more superficial layers, and especially Brodman's third layer, appear to be more easily affected than the deeper, older layers. On the other hand, the phylogenetically older portions of the brain, the medulla and midbrain appear to be affected to a much more limited degree.

(b) *Neuroglia.*—All elements of the glial tissue react to the damage sustained by the neurones in prolonged hypoglycaemia. In the published reports attention is usually devoted to the microglia, the reaction of which is usually of a proliferative type, as shown by Ferraro and Jervis (1939*a* and 1939*b*), Leppien and Peters (1937), and Scherb and Stone (1938). The reaction may, however, be of a degenerative kind. Ferraro and Jervis (1939*b*) had one case in which the neuroglia showed amoeboid changes and clasmatodendrosis throughout the entire cortex. Hypertrophic changes in the microglia and red cells were observed in areas of major destruction of the neurones. MacKeith and Meyer (1939) and Lawrence, Meyer and Nevin (1942) have drawn attention to the marked changes which occur in the macroglia in addition to those to which the microglia is subject. The use of Holzer and Globus-Cajal preparations is necessary to show fully the proliferation of the macroglia, and the use of Nissl's stain only by most other workers probably accounts for the little attention the macroglia have received, as they do not stain well with the latter stain. The outstanding feature of MacKeith and Meyer's (1939) case was the great mobilization and proliferation of the macroglia affecting mainly the sub-pial layer, and to a varying degree the white cerebral and cerebellar matter and the globus pallidus.

(4) *The Blood Vessels of the Brain.*

Two of Ferraro and Jervis's (1939*a*) 5 cases showed no changes either macroscopic or microscopic in the blood vessels, but these cases are exceptional and difficult to explain. In most of the reported cases all the coats of the arteries appear to be affected, but the heaviest incidence of damage falls upon the endothelium [Cammermayer (1938), Ferraro and Jervis (1939*a*, 1939*b*), Gralnick (1941), Jansen and Waaler (1940), Kastein (1938*a*, 1938*b*, and 1938*c*) and Salm (1937)]. The walls of the arteries become greatly thickened owing to proliferation of the cells with narrowing or even obliteration of the lumen. This proliferation is most marked in the endothelium, but it is also shared by the adventitial cells. The nuclei are swollen, and the chromatin granules are darkly stained and increased in numbers. Some cells show varying stages of karyokinesis. Thrombi, secondary to the proliferation of the intimal cells, are frequently seen, as is also diapedesis of both erythrocytes and leucocytes. Perivascular haemorrhages also occur by rhexis. Cammermayer (1938), MacKeith and Meyer (1939) and Lawrence, Meyer and Nevin (1942) also found pseudo-calcification in the media of the pallidal vessels. The degree of vascular change is in direct proportion to the degree of change

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in the neurones and is most marked in the areas of greatest devastation, in which many of the neurones have been completely destroyed. It is this close association between the degrees of vascular and neuronic change which has led several authors to postulate a vascular cause for the changes in the nerve cells. Ferraro and Jervis (1939*a*, 1939*b*) noted that the degree of vascular damage was also directly proportional to the quantity of insulin the patient had received, and found extreme vascular damage only in cases which had received very high doses of insulin.

Another change noted by most of the above authors is that of neoformation of blood capillaries, and here again the process was in direct proportion to the amount of cellular damage in the nervous system.

As regard the veins, several authors have found thrombosis affecting veins of various sizes, while Kastein (1938*c*) describes a case in which the superior longitudinal sinus was thrombosed.

(B) *Changes in Systems other than the Central Nervous System.*

Jansen and Waaler (1940) and MacKeith and Meyer (1939) appear to be the only authors who have made a detailed study at autopsy of organs other than the brain in fatal cases of prolonged coma. This is unfortunate, as such a study would probably shed some light on the problem as to whether the vascular or neuronic changes in the brain are primary. If the vascular changes were found in all the capillaries of the body the vascular hypothesis might be true, whereas if it were found that they were restricted to the brain, it would be presumptive evidence that the neuronic damage was primary and the vascular changes secondary in character.

(1) *Heart.*

Jansen and Waaler (1939) found only slight changes in the myocardium, while MacKeith and Meyer (1939) noted that the cavities were enlarged with flattened columnae carneae. No microscopical examination was apparently made in either case.

(2) *Lungs.*

Any changes in the lungs which might be due to the action of the insulin are usually masked by the terminal congestion of cardiac origin or pneumonia from which the patients finally die [Jansen and Waaler (1940), Salm (1937)]. Cammermayer (1939) noted the presence of " pneumonic infiltration," while Timmer (1938) found congestive haemorrhages. These were apparently not investigated microscopically, and it is interesting to speculate whether they were of the same nature as the haemorrhages usually found in the brain and described above.

(3) *Liver.*

Fatty degeneration of the liver was noted by Cammermayer (1939), Jansen and Waaler (1940), Kastein (1938*c*) and Timmer (1938). MacKeith and Meyer (1939) found only " very great congestion."

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(4) *Pancreas.*

Jansen and Waaler (1940) found considerable change in the pancreas, but ascribed it to post-mortem autolysis. In MacKeith and Meyer's (1939) case there was no superficial evidence of disease of this organ.

(5) *Suprarenal Glands.*

The only reports of examination of the suprarenal glands are those of Schereschewsky, Mogilnitsky and Gorjaewa (1929) and Jansen and Waaler (1940), who in 4 cases found a large increase in the lipoid content of the cortex. This finding is of interest in view of the close association of the suprarenal cortex with carbohydrate metabolism, and of the administration by several authors of the hormone of the suprarenal cortex to patients suffering from post-hypoglycaemic coma.

(6) *Spleen.*

Salm (1937) noted that the spleen was moderately enlarged in one of his cases.

(7) *Kidneys.*

MacKeith and Meyer (1939) found on microscopic examination of the kidneys that they showed "widespread ischaemic degeneration of the glomerular arterioles and capillaries." There were numerous areas of cortical necrosis, corresponding to whitish patches already seen with the naked eye. These were probably secondary to the severe arteriolar degeneration. The kidney changes were recent; pyelonephritis could be excluded, but the authors were doubtful as to their significance. It may be that they were analogous to the changes seen in the cerebral blood vessels, and that the areas of cortical necrosis correspond to the areas of neuronic devastation so frequently found. If this explanation be correct, the vascular theory as to the primary cause of the changes in the brain in prolonged coma would be confirmed.

(c) *Brain Pathology in Animal Experiments in Hyperinsulinism.*

The results in experiments on animals, usually dogs, cats and rats, given large divided doses of insulin over periods of days and weeks approximate so closely to the results found at post-mortem examination of patients who have died from prolonged coma during Sakel's treatment that no purpose would be served by reviewing the literature on the subject in detail. Instead, attention will be concentrated on any additional information which may be elicited under the more controlled conditions under which animal experiments can be conducted. The following papers have been consulted for this study: Schereschewsky, Mogilnitsky and Gorjaewa (1929), Stief and Tokay (1932), Dunner, Ostertag and Thanhauser (1933), Tani (1935), Schmid (1936), Baker and Lufkin (1937), Sherril and MacKay (1937), Massazza (1938), Weil, Liebert and Heilbrunn (1938), Accornero (1938), Roizin (1939), Baker (1939), Appel,

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Alpers, Hastings and Hughes (1939), Winkelman and Moore (1940), Finley and Brenner (1940), Gellhorn, Packer and Feldman (1940), Tyler and Ziskind (1940) and Ziskind and Tyler (1940).

Two factors which the results of animal experiments appear to elucidate are: (1) the possibility that the changes in the central nervous system described by various authors following fatal hyperinsulinism may be due to post-mortem changes, and (2) the relationship between the dosage of insulin employed and the degree of cerebral damage found at autopsy.

Baker and Lufkin (1937) gave insulin to rabbits under similar conditions to those of Sakel's hypoglycaemic treatment and killed the animals 5 days after the cessation of treatment. Microscopic examination revealed "no cell alterations of pathological significance and only an occasional haemorrhage into the brain or meninges. Our experimental observations would, therefore, seem to add weight to our impression that in the human cases, the cellular alterations were most likely of a post-mortem nature." Against this, however, we have the reports of a number of authors, e.g. Weil, Liebert and Heilbrunn (1938), Stief and Tokay (1932 and 1935), Finley and Brenner (1940), Winkelman and Moore (1940) and Roisin (1939), who found marked pathological changes in brains which had been fixed in formalin immediately the animal died. As in the case of Schmid (1936), Baker and Lufkin found such little evidence of abnormality owing to the low dose of insulin employed, and to the fact that their animals did not die in hypoglycaemia.

Several authors discuss the relationship between the dosage of insulin, the severity of hypoglycaemic symptoms and the degree of cerebral damage found post-mortem. Tani (1935) found that the severity of the post-mortem changes did not run parallel with the number of fits the animal had had during hypoglycaemia. In some cases with 10 fits no changes were found, while in others severe changes were found after only a few fits. Tani believes that this difference is related to differences in degree of curvature of the stem arteries. Appel *et al.* (1939) also failed to find such a relationship; one animal which had 56 convulsions showed no post-mortem changes in the brain, while others who had had fewer convulsions showed moderate degrees of ischaemia. Similarly, these authors found no direct relationship between the dosage of insulin employed and the severity of the post-mortem changes. Weil, Liebert and Heilbrunn (1938) found such a relationship, and thus rabbits which "received the largest number of units also showed the most marked histopathological changes. With doses up to approximately 60 units visible disease of the neurones was not produced; from 70–150 units somewhat more marked changes were seen, and with from 200–400 units severe damage was produced. The number of seizures alone is without significance as an indicator of the histopathological changes. What counts is the cumulative effects of repeated injections of large single doses of insulin."

The finding that the number of hypoglycaemic convulsions bears no relation to the degree of cerebral damage is in harmony with the work of Winkelman and Moore (1940), who found that even large numbers (up to 20) of cardiazol-induced convulsions produced little or no change microscopically in the central nervous system.

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Tyler and Ziskind's results agree with those of Weil, Liebert and Heilbrunn (1938), as they found that the larger the dose of insulin used, the greater was the incidence of brain damage found post-mortem. "However," these authors add, "irrespective of the insulin dose, brain damage did not occur unless the animals were kept in the 'medullary stage' of hypoglycaemia for at least 100 minutes." This time-factor in the production of cerebral damage by hypoglycaemia appears to have been investigated by Tyler and Ziskind only, other authors taking account solely of the dosage of insulin employed. In the same year Ziskind and Tyler (1940) produced 3 groups of animals showing varying degrees of cerebral damage by the use of increasing doses of insulin. The groups were: (1) Those with variable degrees of cortical damage only; (2) thalamic preparations; and (3) midbrain preparations. The authors comment: "The demonstration of a gradient effect by insulin on the central nervous system may have a very significant bearing on insulin-shock treatment. The same effects as those now obtained may occur with milder but more prolonged degrees of hypoglycaemia, capable of affecting the higher centres but sparing the lower medullary centres. This would remove the present hazards of the treatment." Unfortunately, this is not borne out by experience, as Cases 1 and 2 of prolonged coma reported above show. For want of a more definite standard, it may be said that it is the total number of milligram/minutes of hypoglycaemia to which the tissues are subject which determines the degree of cerebral damage, and a moderate degree of hypoglycaemia unduly prolonged will have a great, if not greater adverse effect as a large dose acting for a correspondingly shorter time.

It is interesting to note that Schereskewsky, Mogilnitsky and Gorjaewa (1929) found many degenerative changes in the suprarenal glands, in addition to those in the nervous system, including the ganglion cells and neurones of the sympathetic system.

(D) *Causes of Brain Damage Following Hyperinsulinism.*

A number of theories have been advanced as to the cause of the pathological changes in the brain following hyperinsulinism.

(1) The *vascular theory* is that the blood vessels are primarily affected by the hypoglycaemia, and as a result of the endothelial proliferation, venous and capillary thromboses, perivascular exudation and diapedesis of red blood corpuscles, the blood supply to the neurones is interfered with, and the cells undergo changes varying from slight swelling to necrosis as a result. This theory is subscribed to by Doring (1938), Ferraro and Jervis (1939*a*, 1939*b*), Jacob (1939), Jansen and Waaler (1940), Leppien and Peters (1937) and Kastein (1938*b*), although in another paper (1938*c*) the last author prefers a "toxic-metabolic" origin. In favour of the vascular hypothesis is the focal character of the pathological changes, which often have a definite circulatory distribution, although in animal experiments Winkelman and Moore (1940) and Stief and Tokay (1932, 1935) found that almost every cell in the nervous system was affected.

(2) The *anoxic theory* is similar to the above, but attributes the pathological changes to intracellular anoxia rather than to diminished oxygenation due

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to a reduced blood supply from the affected blood vessels. MacKeith and Meyer (1939), Ferraro and Jervis (1939*a*, 1939*b*), Weil, Lieberť and Heilbrunn (1938) mention this hypothesis, which is based on the histological similarity between the effects of hypoglycaemia, and anoxia. Lawrence, Meyer and Nevin (1942) review points of similarity between the two conditions, but as these authors point out, it has been abundantly shown, e.g. Damashek, Myerson and Stephenson (1935) and Himwich, Bowman, Wortis and Fazekas (1937), that in hypoglycaemia there is no lack of oxygen in the blood, but an inability on the part of the tissues to utilize that oxygen owing to a deficiency of glucose in the cells resulting from the hypoglycaemia.

(3) The *toxic-metabolic theory* mentioned by Kastein (1938*c*), Ferraro and Jervis (1939*b*) and Jacob (1939) is that the insulin has a direct histotoxic action on the cells of the nervous system, but in the absence of experiments upon the effects of insulin upon isolated tissues, this remains an hypothesis.

(4) The *oxyachrestic theory* has already been mentioned in connection with the anoxic theory. The word oxyachrestia has been coined by Lawrence, Meyer and Nevin (1942) to emphasize that although the blood contains sufficient oxygen in hypoglycaemia, the tissues are unable to utilize the oxygen owing to a deficiency of the substrate-glucose. This possibility was mentioned by Ferraro and Jervis (1939*a*) among other authors. The word oxyachrestia is inadequate, as it gives no indication as to the cause of the cell's inability to use oxygen. A better term would be *aglucia*, as aglucaemia is already used for an absence of glucose from the blood, so aglucia would refer to an absence of glucose from the tissue-cells (*cf.* anoxaemia—anoxia). Terminological finesse apart, the theory has probably more supporting evidence than those given previously. This evidence will be reviewed in the section on Clinical Pathology, as a considerable amount of work has been done on cellular respiration in hypoglycaemia, especially by Himwich, Wortis and their associates.

It may be noted in passing that all the theories outlined above seek the cause of the pathological changes in the brain following hypoglycaemia in the brain itself, either in the neurones or the blood vessels. This is probably because detailed post-mortem attention has usually been restricted to the brain, especially in human subjects. As has been mentioned above, only two authors, MacKeith and Meyer (1939) and Jansen and Waaler (1940) give detailed reports of the examination of other organs. Yet hypoglycaemia of the severity met with in Sakel's treatment probably affects all tissues throughout the body, and it may well be that the *cause* for the pathological changes in the nervous system lies, not in that system, but in some other system in the body. This becomes the more possible when the complexity of carbohydrate metabolism is borne in mind. It is interesting to note in this connection that Jansen and Waaler (1940) and Schereschewsky, Mogilnitsky and Gorjaewa (1929) found degenerative changes in the cortex of the suprarenal glands after hyperinsulinism, and in view of the part the adrenal cortex is now known to take in carbohydrate metabolism, it may be that the cause of the cerebral changes may be found in the suprarenal gland and not in the brain. Certainly in future post-mortem examinations in cases of prolonged non-hypoglycaemic coma, a detailed microscopic examination should be made of every organ in the body.

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In view of the marked *biochemical* changes which occur in hypoglycaemia and which have been fairly well studied (see next section), and the possibly equally marked biophysical changes which have scarcely been investigated, it is possible that the cause of the pathological changes following hypoglycaemia can never be fully understood from a study of the resulting morbid anatomy, but the study of such morbid anatomy should be as comprehensive as possible.

(2) Clinical Pathology.

In considering the clinical pathology of prolonged coma, the study of the physiological changes which occur during hypoglycaemia is as important as the study of any abnormalities found during the prolonged coma itself. This is because prolonged coma is the end-result of one or more processes which have been going on while the patient has been in hypoglycaemia, and an examination of those processes rather than of the end-result itself may yield the clue as to the cause of the condition. Clinical pathological findings which have been reported during prolonged coma will, therefore, be considered first, after which the physiological changes induced by hypoglycaemia will be reviewed.

Attention has been directed chiefly to the behaviour of the various constituents of the blood, cerebrospinal fluid, etc., during prolonged coma, and in the following review the constituents which have been reported upon will be described separately.

(A) *The Blood.*

(1) *Blood Sugar.*

Soon after prolonged coma was first described, it was recognized that the condition was not accompanied by a low blood sugar, as pointed out by Robinson and Robinson (1940). Very high blood-sugar values such as 280 mgm. per cent. [Molony and Honan (1937), Wortis and Lambert (1939)], 520 mgm. per cent. [Theato (1939)], 295 mgm. per cent. [Horwitz *et al.* (1938)], 576 mgm. per cent. [Ribeiro and di Lascio (1939)] and 230 mgm. per cent. [James, Freudenberg and Cannon (1938)] have been reported. It must be noted, however, that these high blood-sugar values have been found at examinations undertaken at sporadic intervals; frequently only a single estimation has been made during the course of the prolonged coma. Braestrup (1939) found a blood sugar of 155 mgm. per cent. 90 minutes after intravenous interruption, but this had dropped to 30 mgm. per cent. 75 minutes later, so that a high blood-sugar finding is not invariable in the condition. The only report in the literature in which regular blood estimations at fairly frequent intervals were done is that of Proctor and Easton (1942), who found that the blood sugar fluctuated rapidly between 46 mgm. per cent. and 320 mgm. per cent., and did not settle to within normal limits until the patient's clinical condition had markedly improved. It is possible that more intensive investigations would reveal a similar condition in other patients. It is indicative of a serious derangement of carbohydrate metabolism, and a satisfactory explanation of it is difficult to find. On the basis of Himsworth's (1939) " head of pressure "

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theory of the function of the blood-sugar level, it might be thought that the previously glucose-starved cells may be able to utilize glucose supplies under high pressure, but that the attainment of the high level sugar necessary temporarily exhausts the blood-sugar level-maintaining mechanism, so that the blood sugar drops. As the blood-sugar level-maintaining mechanism recovers, so the blood sugar rises to a high level again, only to fall once more as the mechanism again becomes exhausted. This would account for the rhythmical rise and fall in the blood sugar dramatically shown in the chart in Proctor and Easton's report.

(2) *Blood Chloride.*

Compared with the normal 365 mgm. per cent. [Samson Wright (1945)] the blood chloride usually appears to be reduced in prolonged coma. Goldman (1940) reports a "relatively low" blood chloride, while Young, Young and Roucek (1937) found a value of 275 mgm. per cent.; Kant (1940), 209 mgm. per cent. These low values are probably due to excessive loss of chlorides in the profuse perspiration which is such a characteristic of post-hypoglycaemic coma, and indicates the need for maintaining an adequate chloride intake either by mouth or intravenously.

(3) *Blood Urea.*

In the 3 cases in which the blood urea has been estimated, it also appears to be on the low side. Goldman (1940) found a value of 19 mgm. per cent., Scherb and Stone (1938) one of 24 mgm. per cent., and O'Neill (1938) one of 16 mgm. per cent.

(4) *Blood Calcium and Phosphorus.*

In view of the tetanic nature of the myotonic spasms in prolonged coma, the carpo-pedal spasm which is present during the spasms and the ease with which they can be initiated by external stimuli, it might be thought that they were due to a calcium deficiency. Goldman (1940), however, who investigated the levels of blood calcium and phosphorus in prolonged coma, found only values within normal limits.

(5) *Blood Carbon Dioxide.*

Franke (1937) reported that in one of his cases of prolonged coma the carbon dioxide combining power of the blood was 50 volumes per cent., while in a case of Horwitz, Blalock and Harris (1938) the much lower figure of 22 volumes per cent. was found.

(6) *Arterio-venous Oxygen Difference.*

No reports have been published on this important factor in prolonged coma following Sakel's treatment, but Himwich, Bowman and Fazekas (1940) investigated it in a diabetic who died in prolonged coma following an overdose of insulin. The average arterio-venous difference in the oxygen content

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of the cerebral blood was 2·76 volumes per cent., compared with the normal difference of 7·43 volumes per cent. This low value is similar to that found during insulin hypoglycaemia, and indicates that in prolonged coma the cerebral tissues are unable to utilize the oxygen supplied to them despite the fact that the necessary glucose substrate is now circulating in the blood.

(7) *Blood Concentration.*

Quantitative studies in the concentration of the blood in prolonged coma do not appear to have been made, but, amongst others, Goldman (1940) "early recognized that blood concentration was a feature of this reaction because the blood drawn for sugar determinations was thick and dark." Probably the excessive loss of fluid in the profuse perspiration and salivation to which patients in prolonged coma are subject is sufficient cause for the haemoconcentration.

(8) *Blood Counts.*

There appears to be a mild leucocytosis in post-hypoglycaemic coma. Murphy (1939) found a white cell count of 15,000, with 78 per cent. polymorphonuclears, 12 per cent. large lymphocytes, 8 per cent. small lymphocytes and 2 per cent. basophils. McKendree (1938) reported a white cell count of 13,400 with 84 per cent. polymorphonuclears and 16 per cent. lymphocytes. Wechsler (1944) found a leucocytosis of 10,800, and Theato (1939) one of 20,600. Reports of erythrocyte counts are restricted to one by McKendree (1937), whose patient had a haemoglobin value of 70 per cent. and 3,520,000 erythrocytes per c.c., and one by Theato (1939), in whose patient the figures were 90 per cent. and 5,000,000 respectively.

(9) *Blood Culture.*

Murphy (1939) cultured some blood from one of his patients in post-hypoglycaemic coma but the result was negative.

(B) *The Cerebrospinal Fluid.*

(1) *Pressure of C.S.F.*

With a few exceptions the pressure of the cerebrospinal fluid has been found to be normal, but unfortunately the number of manometric readings reported in the literature has been few, and most authors appear to have estimated the pressure from the rate at which the fluid escaped at the time of lumbar puncture. The following authors found normal C.F.S. pressures: McKendree (1938), O'Neill (1938), Horwitz, Blalock and Harris (1938), Goldman (1940), Cleckley and Templeton (1941), Gillman and Parfitt (1938) (one case), Read, Heilbrunn and Liebert (1939), Wortis and Lambert (1939), and Gralnick (1941), who did manometric readings at regular intervals throughout the course of a prolonged coma, found that the pressure was "low." On the other hand, Murphy (1939), Binzley and Anderson (1938), Braestrup (1939), and Proctor and Easton (1942) found slightly increased pressures. These

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last findings may have been due to the patient being in a state of muscular tension when the lumbar puncture was performed. It appears, however, that the intracranial pressure is not raised in prolonged coma, a finding which is all the more interesting in view of the quietening effect which withdrawal of 10–20 c.c. of cerebrospinal fluid has upon a patient in the restless phases of the condition.

(2) *C.S.F. Sugar.*

Compared with the reports of Horwitz, Blalock and Harris (1939) and Goldman (1940), who found no increase in the C.F.S. sugar, high values were found by the following authors: Molony and Honan (1937), 300–360 mgm. per cent.; Murphy (1939), 122 mgm. per cent.; James, Freudenberg and Cannon (1938), 300 mgm. per cent.; Cleckley and Templeton (1941), 100 mgm. per cent.; Binzley and Anderson (1938), 105 mgm. per cent.; Gillman and Parfitt (1938), 135 mgm. per cent.; Ribeiro and di Lascio (1939), 223 mgm. per cent.; Abely and Feuillet (1942), 114 mgm. per cent.; but Braestrup (1939) reported the low figure of 55 mgm. per cent.

These very high values are often higher than the level of the blood sugar [Molony and Honan (1937)], and probably indicate the disturbed condition of carbohydrate metabolism in prolonged coma [Proctor and Easton (1942)].

(3) *Other C.S.F. Constituents.*

Brief reports on other constituents of the C.F.S. such as the chloride and protein content have appeared, e.g. Kant (1940), O'Neill (1938), but they appear to be present within normal limits.

(c) *The Urine.*

As would be expected with the abnormally high blood-sugar values found in prolonged coma, several workers, e.g. Scherb and Stone (1938), O'Neill (1938), Horwitz, Blalock and Harris (1938), Binzley and Anderson (1938), Gillman and Parfitt (1938), found sugar (up to 4 per cent.) in the urine, but as a rule, acetone and diacetic acid were absent. Apart from this finding and again indicative of deranged carbohydrate metabolism, the urine appears to be normal.

From the above review, it will be seen that investigations into the chemical pathology of prolonged coma have been inadequate both in range and intensity. The only clue to the cause of the condition which they afford is that there is undoubtedly a marked derangement of carbohydrate metabolism as shown by the widely fluctuating blood sugar [Proctor and Easton (1942)], the reversal of the usual ratio of the sugar levels in the blood and cerebrospinal fluid and the presence of sugar in the urine. Carbohydrate metabolism is not yet fully understood, but the endocrine system certainly plays a part in it, and it may be that the cause of post-hypoglycaemic coma lies in the effect of prolonged hypoglycaemia on some gland such as the pituitary or suprarenals, rather than on the neurones of the brain. As a result of such action, the

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gland is unable to function properly when glucose is administered, carbohydrate metabolism is deranged, the brain, dependent as it is entirely upon carbohydrate for its metabolism, is unable to utilize the glucose now circulating in the blood and the patient remains in coma.

VIII. Physiological Changes in Hypoglycaemia.

It has been shown in the preceding section that the only positive finding in the chemical pathology of post-hypoglycaemic coma is that there is a profound derangement of carbohydrate metabolism which continues in spite of the administration of adequate carbohydrate. As the carbohydrate mechanism returns to normal, so the patient's clinical condition improves (Proctor and Easton, 1942). Too much attention has probably been paid to the effects of hypoglycaemia upon the nervous system, and too little to its effects upon the known stages of carbohydrate metabolism. In this review of the physiological changes in hypoglycaemia an attempt will be made to determine whether an adequate cause can be found for the derangement of carbohydrate metabolism. It would appear that this derangement is primary, and that the irreversible changes which are found in the brain in prolonged coma are secondary to it, but that once those irreversible changes have occurred *nothing* can reverse them, and that the patient's clinical improvement mentally is due to undamaged portions of the brain taking over the functions of the cells in which irreversible changes have taken place. It will be seen, therefore, that methods of therapy for prolonged coma which are based upon the pathological findings in the brain are unlikely to be successful in view of the irreversibility of the changes found there. If the exact point at which the carbohydrate mechanism becomes deranged can be found, a form of therapy might be devised to correct matters at that point. Better still, means might be found by which the derangement could be avoided.

Much remains unknown about carbohydrate metabolism, but the following scheme, adapted from Samson Wright (1945), summarizes our present knowledge.

(1) *Intestine*, glucose and amino-acids are absorbed and pass to the liver.

(2) *Liver* converts—

(i) Glucose → glycogen → glucose.

(ii) Amino-acids → non-nitrogenous residues and urea.

(3) *Blood glucose* formed from liver glycogen and non-nitrogenous residues of amino-acids.

(4) *Insulin* acts on—

(i) Liver, stimulating glycogen formation.

(ii) Liver, inhibiting glucose formation from non-nitrogenous residues of animo-acids.

(iii) Tissues, increasing glycogen storage and carbohydrate utilization.

(5) *Adrenaline, sympathetic N.S., thyroxine* stimulate conversion of liver glycogen to glucose.

(6) *Adrenocortical hormone* stimulates glycogen formation in liver and inhibits new glucose formation.

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(7) *Diabetogenic hormone of pituitary gland* acts on—

(i) Liver, stimulating conversion of glycogen into glucose.

(ii) Liver, inhibiting new glucose formation from non-nitrogenous residues.

(iii) Tissues, inhibiting carbohydrate utilization.

It will thus be seen that carbohydrate metabolism is an extremely complex process. Five endocrine glands and the liver are actively concerned in the cycle, and it may be that the effects of prolonged hypoglycaemia upon the endocrine glands in particular impair their efficiency even after glucose has again been administered, and account for the derangement of carbohydrate metabolism which has been found in post-hypoglycaemic coma.

As in the review of the pathological changes during post-hypoglycaemia, the physiological changes will be described under the headings of the tissue constituents and processes affected.

(A) *Cerebral Metabolism.*

(1) *Oxygen Uptake of the Brain.*

It is known that the brain utilizes only carbohydrate in its metabolism, and that its respiratory quotient is consequently 1·0. Himwich and his associates [Himwich, Bowman, Wortis and Fazekas (1937, 1939*a* and 1939*b*); Himwich and Fazekas (1937*a*, 1937*b*); Himwich, Frostig, Fazekas and Hadidian (1939); Himwich, Frostig, Fazekas, Hoagland and Hadidian, (1939); Himwich, Martin, Alexander and Fazekas (1939); Himwich, Hadidian, Fazekas and Hoagland (1939); Wortis, Bowman, Fazekas and Himwich (1941)] have investigated cerebral metabolism during hypoglycaemia by comparing the differences between the blood in the internal carotid artery and that in the internal jugular vein. A detailed analysis of these authors' work cannot be attempted here, but in general it may be said that their results confirm the observations of Damashek, Myerson and Stephenson (1935), who found a diminished utilization of both glucose and oxygen during hypoglycaemia. Himwich and his co-workers conclude that the inability of the brain to utilize the oxygen supplied to it as evidenced by the reduced arteriovenous difference is due to the deprivation of the substrate glucose owing to the low blood sugar, so that the condition is not a true anoxaemia. There is sufficient oxygen available in the arterial blood, but the glucose-depleted brain cells are unable to utilize it. Himwich holds that in severe hypoglycaemia such as is met with in Sakel's treatment, even the intrinsic glucose of the brain cells is used up, and this may account for the irreversible changes which occur in prolonged coma. The work of those authors is an extension of that of Olmsted and Taylor (1924), who, however, ascribed their results to anoxaemia, and has been confirmed by Loman (1940, 1941), Rosenberg (1939) and Wortis and Goldfarb (1940*a*, 1940*b*, 1942).

It is possible that the diminished utilization of oxygen might be counteracted by an increased blood flow, but Leibel and Hall (1938), Lennox and Gibbs (1932), Gibbs, Gibbs and Lennox (1935) and Lennox, Gibbs and Gibbs (1938) could find no evidence of any increase in the blood flow. Yesinick

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and Gellhorn (1939–40), Gellhorn (1938), Gellhorn, Darrow and Yesinick (1939), Gellhorn, Ingraham and Moldawsky (1938*a*, 1938*b*), Yesinick and Gellhorn (1939–40) and Gellhorn, Packer and Feldman (1940), working on the association between hypoglycaemia and anoxaemia, found that hypoglycaemia potentiates the increased blood pressure response to intracranial pressure, which if the intracranial pressure were raised in the hypoglycaemia of Sakel's treatment, would cause a greater flow to the brain. As has already been seen, however, the intracranial pressure is not so raised, so that the brain does not receive any extra blood for this reason. It therefore appears that as far as the brain is concerned, one of the main effects of hypoglycaemia is to deprive the neurones of their glucose, without which they cannot utilize the available oxygen. It is interesting to note in this connection that Holmes (1930) pointed out that the dependence of the neurones upon glucose for oxidation is far greater than that of other parts of the nervous system, such as the white matter.

It is interesting to speculate whether this state of " aglucia " of the brain cells is primary to the numerous other changes, such as electrolytic changes, seen in the body in hypoglycaemia, whether the electrolytic changes are not due to the effect of the hypoglycaemia on some other organ such as the suprarenal cortex, and whether it is the aglucia or the electrolytic changes which prevent the cerebral metabolism from returning to normal in prolonged coma.

(2) *Mineral Content of the Brain.*

Liebert and Heilbrunn (1940) studied microincinerated sections of the brains of rabbits who had been treated with insulin along the lines of Sakel's treatment, and found that, while there was no change in the total ash content of the brain, marked changes occurred in the ganglion cells in the form of dust formation, hypomineralization, vacuolation, or complete demineralization. The changes were especially prominent in the cells of Ammon's horn. There was an increase in the mineral content of the glial tissue. Biopsy showed that these changes were present after an insulin convulsion, but became reversed after a certain time.

Yannet (1939), experimenting on cats, concluded that hypoglycaemia caused a shift of potassium from the cell to the extracellular tissues accompanied by a marked shift of intracellular water, and suggested that the osmotic equilibrium is maintained under these conditions by a transfer of sodium across the cell membrane.

(3) *Water Content of the Brain.*

As mentioned above, Yannet (1939) found that water passed from the interior of the cell to the extra-cellular spaces in hypoglycaemia but later returned as sodium permeated into the cell. He was unable to find any changes in the total water of the brain. This conclusion was also reached by Hall (1938) from experiments conducted by Sniffen and Irwin.

(4) *pH of Brain.*

This has been studied by Marshall, McCullock and Nims (1939), who found that the pH of cerebral cortex remained unchanged for from 60–90 minutes

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following the injection of insulin, after which it underwent a series of striking fluctuations, consisting of an abrupt rise followed by a slower fall. These fluctuations recurred at short intervals, and in the intervening periods the pH was relatively constant. No corresponding changes in the pH of the blood could be found, and as the chemistry of the changes is unknown the authors could offer no explanation for them.

(5) *Permeability of Brain Cells.*

Spiegel and Spiegel-Adolph (1939) found a marked increase in the permeability of the walls of the brain cells, and that in general the change was proportional to the duration of hypoglycaemia. This increased permeability of the cell wall helps to explain the movements of electrolytes to and from the cell, and as the authors point out, " repeated injuries of the cell membrane may eventually result in more severe lesions of the cells, as shown by the histological examination after prolonged convulsion treatment."

(B) *Changes in the Blood.*

The changes in the constituents of the blood during hypoglycaemia have been reviewed by Katzenelbogen (1940), whose findings may be summarized as follows : There is, of course, the fall in the blood sugar to which further reference is unnecessary. The levels of potassium, urea-nitrogen and amino-acids fall steadily throughout the period of hypoglycaemia, while that of inorganic phosphorus falls for the first 2 hours and then rises ; calcium and magnesium appear to be unaffected, while there is conflicting evidence as to the behaviour of the sodium and chlorides.

(C) *Changes in the Cerebrospinal Fluid.*

The cerebrospinal-fluid sugar follows, but lags considerably behind the blood sugar [Day and Niver (1937) ; Day, Niver and Greenberg (1938)]. After interruption of the hypoglycaemia with glucose, the C.S.F. sugar lags behind the blood sugar in its return to normal, so that the patients' return to consciousness may be associated with a more or less marked hypoglycorrhacia.

(D) *Electroencephalographic Changes.*

Himwich, Frostig, Fazekas, Hoagland and Hadidian (1939) and Himwich, Hadidian, Fazekas and Hoagland (1939) found that there was a direct relationship between the frequency of the alpha waves and the cerebral oxygen consumption, both declining during hypoglycaemia and increasing after the administration of glucose. The delta index displays an inverse relationship, and becomes augmented during the period of diminished oxygen utilization of the brain. This work has been confirmed, *inter alia*, by Gibbs, Williams and Gibbs (1940).

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(E) *Changes in Other Organs.*

These changes have already been considered in the section on the pathology of post-hypoglycaemic coma. They have been studied by Tannenberg (1939), whose work has been confirmed by other authors. Tannenberg found that insulin given to rabbits along the lines of Sakel's treatment produced :

(1) *In the heart and skeletal muscles*—definite hydropic changes. The posterior wall of the left ventricle and its papillary muscles were the site of election in the heart, as were the iliopsoas and thigh muscles among the skeletal muscles. The changes consisted of broken muscle fibres of all stages. Most of the changes were considered reversible, but small areas of necrotic cardiac cells were found.

(2) In the *liver* two types of reaction were found :

(*a*) Where the liver was able to release all the glycogen synthesized from various sources before and after the administration of insulin the fall in the blood sugar was not very marked, and damage to vital organs did not result.

(*b*) Where the liver retained the available carbohydrate as glycogen and locked it up, particularly in the centres of the lobules, which became overladen, with constriction of the capillaries, the blood sugar fell to low levels and the heart and musculature showed severe damage. Small areas of necrosis in the liver were observed especially in rabbits treated with high doses of insulin. Terron and Malesani (1939), using the Weltmann and Taka-Ara reactions, were unable to detect any dysfunction of the liver, but in view of the unreliability of liver function tests, Tannenberg's results would seem to be more accurate.

(3) As mentioned earlier, a number of authors have found changes in the cortex of the suprarenal gland which are of interest in view of the ionic changes found in hypoglycaemia, and the probable part which the adrenal cortex plays in the control of ionic changes in the tissues.

From the above summary it will be seen that the only factors which emerge from a study of the physiological changes in hypoglycaemia and which may help in the search for the cause of prolonged coma are :

(1) There is a marked reduction in cerebral metabolism owing to the depletion of the substrate glucose, and, since the brain can only use carbohydrate in its metabolism, prolonged deprivation of glucose may lead to irreversible changes in the cerebral neurones for one of two reasons :

(*a*) Irreversible changes within the neurones themselves.

(*b*) Damage to a part of the carbohydrate controlling mechanism, such as the pituitary gland, sympathetic nervous system, adrenal glands, etc., so that the cerebral neurones are unable to utilize the carbohydrate available in the blood stream after the administration of glucose.

(2) There is a shift of potassium and other electrolytes from the cerebral neurones into the intracellular spaces and glial tissues. A point may be reached

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at which these ionic changes become irreversible for one of two reasons similar to those by which the cells cannot utilize their available glucose :

(*a*) The intracellular ionic changes may have resulted in irreversible changes in the structure of the cell as far as the electrolytes are concerned.

(*b*) The mechanism controlling the ionic balance of the body (e.g. adrenal cortex) may be damaged, so that the ionic intracellular arrangements cannot return to normal.

Until more is known of the nature, site and cause of the irreversible changes which accompany prolonged hypoglycaemia, the exact cause of prolonged coma will continue to elude us.

IX. Symptomatology of Post-Hypoglycaemic Coma.

The description of the symptoms of prolonged coma is made more difficult by the varying degrees of severity of the condition which may be encountered. In mild cases, as Case 2 reported above, the patient merely remains unconscious, no symptoms indicative of focal involvement of the nervous system develop, the temperature is only moderately raised, the general condition remains good, and in a matter of hours or days the patient regains consciousness, and in a comparatively short period shows no signs of mental enfeeblement as the results of his experience.

In more severe cases the picture is different. The temperature is raised considerably, up to 105° F., the pulse varies from 110–160 per minute, and the respiration rate is usually 30–40 per minute. The patient is deeply unconscious. Babinski plantar responses may be present for some hours, but the corneal reflex can usually be elicited. A characteristic feature during the first 24–48 hours of severe prolonged coma is the intense myotonic-clonic spasms, which, beginning gradually, become more and more intense until the patient may assume a position of almost complete opisthotonos. These spasms last about 10 minutes and may recur every 10–15 minutes unless they are controlled by intravenous barbiturate or rebreathing. The patient is doubly incontinent, perspires and salivates freely and may vomit any food given by nasal or oesophageal tube. Gradually, again in a matter of hours or days, the myotonic spasms cease, the Babinski responses disappear, the temperature falls, and the patient slowly regains consciousness, and as he does so various signs and symptoms indicating focal lesions of the brain may become apparent. There may be Jacksonian fits (Wortis and Lambert, 1939), spastic deviation of the head and eyes (Scherb and Stone, 1938), hemiplegias (Read, Heilbrunn and Liebert, 1939), paralysis of the ocular muscles (von Pap, 1937), chewing movements (Kant, 1940), facial paralysis (Binzley and Anderson, 1938). The patient's speech is at first dysarthric and aphasic, but gradually returns to normal. His movements in general are clumsy and unco-ordinated and he walks on a broad base. As his condition improves, memory defects of an organic kind are frequently seen. The commonest of these is Korsakov's syndrome, reported by Milch and Bolles (1938), Horwitz, Blalock and Harris (1938) and Billig and Sullivan (1942) amongst other authors. Other memory defects which may occur are retention defects as reported by Kant (1940),

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whose patient was able to remember remote events but not recent ones, and misidentification of persons (Horwitz, Blalock and Harris, 1938). The rate of improvement depends upon the severity of the prolonged coma, and it may be days, weeks or months before the patient regains his precomatose level. Some, as will be seen, never reach it.

X. Prognosis of Post-hypoglycaemic Coma.

Prolonged coma may end in (1) death, (2) physical recovery with improvement in original psychosis, (3) physical recovery without improvement in the original psychosis, (4) physical recovery with varying degrees of dementia.

The mortality rate in post-hypoglycaemic coma varies within fairly wide limits. Lester (1938–39) had a mortality rate of 16 per cent. in 25 patients, Rivers and Rome (1944) one of 5 per cent. in 51 cases; Goldman (1940), however, had no fatalities among his 23 cases.

Death usually occurs either from supervening pneumonia or from myocardial collapse. The latter is the commonest cause of death, and is probably due to the fact that the myocardium has already been damaged by the hypoglycaemia intentionally induced.

A number of authors, e.g. Rossman and Cline (1937–38), Lester (1938–39), McKendree (1938), Katzenelbogen (1939), Coyne (1940), James, Freudenberg and Cannon (1938), have reported cases which improved very considerably following the development of prolonged coma, and following his own similar experience Kraulis (1937, 1938) produced protracted comas of up to 12 hours' duration, with a view to increasing the effectiveness of Sakel's treatment. Following up Kraulis' work, Billig and Sullivan (1942) and Wortis, Terris and Korr (1942) have intentionally produced prolonged comas, with, they claim, satisfactory results. These comas are, however, not the same as the post-hypoglycaemic comas now being studied, as the patient is given small amounts of glucose periodically during the coma to prevent the hypoglycaemic state from becoming too profound.

As compared with the above, several authors, e.g. Horwitz, Blalock and Harris (1938), Binzley and Anderson (1938) have reported cases in which no improvement in the patient's psychosis occurred after the post-hypoglycaemic coma, and unfortunately there are many cases reported in which the patient's last condition was worse than his first. The likelihood of any patient improving psychiatrically as a result of post-hypoglycaemic coma is too uncertain to justify its induction for therapeutic reasons.

XI. The Treatment of Post-hypoglycaemic Coma.

The widely varying methods of treatment which have been adopted in cases of prolonged coma indicate that a specific remedy for the condition has yet to be found. This is to be expected, since the actual cause of the condition is, as has been shown earlier, still unknown. If it be assumed that the irreversible changes in the neurones of the brain are the primary cause, the exact nature of those irreversible changes is not known. In the absence of fuller

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knowledge of such changes, it is difficult to suggest ways by which they can be influenced. Most authors have approached the problem from a chemical point of view, stressing the part played by glucose in brain metabolism, yet the changes may well be essentially physical and not chemical in nature, and their irreversible character may disappear if the physical milieu of the cells could be changed. If, on the other hand, it is assumed that prolonged coma is essentially due to a breakdown of carbohydrate metabolism, as suggested by the work of Proctor and Easton (1942), the exact point of this breakdown in the cycle of carbohydrate metabolism is unknown, and until it is, a specific remedy for prolonged coma will probably not be found. At present, therefore, treatment for post-hypoglycaemic coma must necessarily be symptomatic—a view insufficiently stressed by most authors.

The forms of treatment which have been tried may be classified as follows :

(1) *Replacement of Tissue-deficiencies.*
   (*a*) Vitamin B_1. (*b*) Nicotinic acid and riboflavine. (*c*) Adrenal cortex hormone. (*d*) Calcium salts. (*e*) Potassium salts. (*f*) Blood transfusion. (*g*) Pitruitrin. (*h*) Insulin.

(2) *Maintenance of the Circulation.*
   (*a*) Administration of fluids. (*b*) Cardiac stimulants. (*c*) Blood-letting. (*d*) Blood transfusion.

(3) *Maintenance of Respiration.*
   (*a*) Oxygen and carbon dioxide. (*b*) Respiratory stimulants.

(4) *Administration of Insulin-antagonistic Substances.*
   (*a*) Adrenaline.

(5) *Lumbar Puncture.*

(6) *Administration of Sedatives.*

(7) *Miscellaneous Forms of Treatment.*

These methods of treatment will now be considered.

(1) *Replacement of Tissue-deficiencies.*

(a) *Vitamin B_1.*—Freudenberg (1937) first asserted that vitamin B_1 was of value in cases of prolonged coma ; his experience was that patients who did not respond to oral glucose promptly awoke on the administration of 2·5 mgm. of thiamine chloride. It is known that in the brains of pigeons with B_1 avitaminosis, pyruvic acid and methyl glyoxal are present. Neither of these metabolites is present in normal brain, and they disappear from the avitaminotic specimens when vitamin B_1 is added. They are similarly present in muscle after hyperinsulinism, so that there would appear to be theoretical justification for Freudenberg's findings, especially as the large amount of carbohydrate usually found in the diet of patients on Sakel's treatment may cause a relative deficiency of vitamin B_1 (Goldfarb and Bowman, 1941). Himwich, Spies, Fazekas and Nesin (1940) found a reduction in the arteriovenous oxygen difference in pellagrous patients similar to that found in the milder stages of hypoglycaemia. Later authors, however, in general have failed to confirm Freudenberg's results. Akos (1939) claimed that the previous

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administration of vitamin B_1 reduced the amount of restlessness during coma, but this could only be partially confirmed by Somerfeld-Ziskind *et al.* (1942). Rossman and Cline (1937–38) and Finiefs (1938*a*) recommend the use of vitamin B_1 in prolonged coma, but Wortis and Lambert (1939), O'Neill (1938), Cleckley and Templeton (1941), Gillman and Parfitt (1938), Ribeiro and di Lascio (1939), Freed and Saxe (1939), Rivers (1941) and the present author found that it did not affect the progress of the coma. Somerfeld-Ziskind *et al.* (1942), using the vitamin orally, intramuscularly and intravenously, found that it did not affect the " arousal from coma " times of 27 patients compared with a control series.

In view of these findings it must be concluded that vitamin B_1 has no specific effect in prolonged coma.

(b) *Nicotinic acid and riboflavin.*—Cleckley and Templeton (1941) gave 150 mgm. nicotinic acid and 15 mgm. riboflavin without apparent effect.

(c) *Adrenal cortex hormone.*—Goldman (1940) found that adrenal cortex hormone (cortin) had a marked quietening effect on two of his cases, but the fact that it was given in one case daily for 10 days indicates that it had no specific effect. The part played by the adrenal cortex in carbohydrate metabolism is a complicated one, and a number of substances have been isolated from it which have varying effects. One substance acts like insulin in promoting glycogen formation in the liver [Samson Wright (1945)], but another [Seyley and Dosne (1939)] counteracts the changes in the blood sugar induced by insulin. Seyley and Dosne believe it has a *stabilizing* effect on the blood sugar, and so might be useful in controlling the fluctuating blood sugar found in prolonged coma. Another action of the adrenal cortex is to stabilize the ionic conditions of the tissues which are disturbed in post-hypoglycaemic coma (Rivers and Rome, 1944). There are, therefore, theoretical grounds for believing that adrenal cortex extracts might be of value in prolonged coma, and a further trial of them would be justified now that stronger extracts of more definite composition are available.

(d) *Calcium salts.*—Calcium salts, usually the chloride, have been given to counteract the alkalosis found in post-hypoglycaemic coma, and are recommened by Finiefs (1938*b*), Murphy (1939), James, Freudenberg and Cannon (1938), and Goldman (1940). Gillman and Parfitt (1938), however, found them to be useless.

(e) *Potassium salts.*—Cleckley and Templeton (1941) gave 2 gm. of potassium chloride in 500 c.c. of saline subcutaneously and found that the convulsions ceased after 30 minutes. Skaug and Hellem (1939), however, found in a case of prolonged coma that the blood potassium was higher than normal, although they found that patients with a " long arousal time " after oral glucose quickly responded to the administration of 0·2 per cent. NaH_2PO_4. They maintain that this enables the sugar to be absorbed from the intestine.

(f) *Blood transfusion.*—Reports on the immediate effect of blood transfusion are not available, but Kubo (1937) states that it saved the patient's life in two of his cases, while Wortis and Lambert (1939) were able to treat the condition with " apparent success " by this means, and James, Freudenberg and Cannon believe it to be " of the utmost value." Wortis, Shaskan, Impastato

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and Almansi (1941) believe that whole blood contains enzymic factors (other than glucose) essential to brain metabolism. In the present author's experience these claims have not been confirmed, and any beneficial results following blood transfusion have probably been due to the support given to the circulation by the administration of a large quantity of fluid. A female patient, who went into prolonged coma following intravenous insulin, strikes a warning note [Spencer (1947)]. Although the bloods were cross-matched microscopically to ensure compatibility, a violent rigor followed by a severe degree of cardiac failure occurred. It is probable that the patient, a multipara, was an Rh-negative subject who was transfused with Rh-positive blood. The patient recovered as her general condition was good when the transfusion was started. Had the general condition been poor, as it frequently is when such patients are transfused, the outcome would probably have been fatal. As a precautionary step all patients undergoing Sakel's treatment should have their blood grouped before treatment commences, and the blood-grouping should include the Rh factor.

(g) *Pituitrin*.—Gillman and Parfitt (1938) gave pituitrin (0·5 c.c.), but it does not appear to have influenced the course of the patient's coma.

(h) *Insulin*.—It is interesting to note that some authors [Molony and Honan (1937), Easton (1938), Ribeiro and di Lascio (1939), O'Neill (1938)] have given further insulin (10–30 units) during prolonged coma in view of the high blood-sugar values obtained. There appears to be no justification for such a step since, as Proctor and Easton (1942) have shown, the blood sugar is probably not consistently high, but fluctuates a great deal. This is probably due to a derangement of the carbohydrate metabolism, as the quantities of glucose usually injected in post-hypoglycaemic coma actually represent quite a small carbohydrate intake, and to inject further insulin probably only serves to delay the stabilization of the carbohydrate metabolism still further.

(2) *Maintenance of the Circulation.*

(a) *Administration of fluids*.—Two schools of opinion exist as to the advisability of giving fluids in cases of prolonged coma. The one advocates giving adequate fluids in order to support the circulation in view of the large amount of fluid lost in the profuse perspiration [Fraser and Sargant (1940), Timmer (1938), Theato (1939), Finiefs (1938*a*), O'Neill (1938)]. As has been shown in the section on morbid anatomy, the heart itself is affected by hypoglycaemia and every care must be taken to maintain the circulation, as the commonest immediate cause of death in prolonged coma is either terminal pneumonia or myocardial failure. Intravenous saline can be of much value in this condition, but it needs to be administered with considerable caution since, as in cases of ordinary diabetic coma, it is possible to overload the heart if too much fluid is given by this route, especially if it be given too quickly. Estimations of blood volume are useful, but in general it may be said that isotonic saline through a stomach tube is safer from a cardiac aspect than large quantities intravenously.

Other authors following O'Neill (1938) have sought to promote dehydration

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instead of administering fluids to counteract the dehydration already existing. Rivers (1941) and Rivers and Rome (1944) used solutions of sodium arabinate, dextrosorbitol, mannitol, styracital and concentrated lyophile serum for this purpose. They claim that "in all instances" clinical improvement was obtained within the hour. The administration of dehydrating substances is based on the presence of intracellular oedema of the brain cells, since at post-mortem many of the cells are found in a swollen condition, and Rivers and Rome hold that as a result of ionic changes there has been a passage of water into the cell which is reversed by the giving of dehydrating substances. Whether such a reversal in the absence of the correction of the ionic imbalance is desirable is open to doubt, as the intracellular oedema may be protective in character. That dehydrated animals do not have convulsions during hypoglycaemia was shown by Drabkin and Ravdin (1930, 1937) but Drabkin and Shilkret (1927–28) found that despite this, dogs which had been given fluids invariably recovered on the administration of glucose, whereas those that had been deprived of water for more than 4 days did not survive. Tyler, Greeley and Drury (1939) found that dehydration also leads to an increase in the basal insulin requirements of the depancreatized dog, which would seem to indicate that dehydration increases the difficulty of stabilizing the carbohydrate metabolism. In the absence of fuller clinical details about Rivers and Rome's (1944) patients, it is difficult to assess the efficacy of their dehydrating methods, and until more conclusive evidence of the value of dehydration is obtained it would seem advisable to continue to give adequate amounts of fluids.

(b) *Cardiac stimulants.*—Theato (1939) regarded coramine as the "chosen remedy" for prolonged coma, giving it in the very large doses of 77 gm. in 12 hours, of which 55 gm. were given in 2 hours. Other authors, e.g. Rossman and Cline (1937–38), Gillman and Parfitt (1938) and Easton (1938) have given it in more usual doses with beneficial effect on the cardiovascular and respiratory systems. While it probably does not, as Theato claimed, have a specific action on the myotonic spasms, it is undoubtedly useful in maintaining the circulation. Other cardiac stimulants which have been used by various authors are: caffeine sodium benzoate [Easton (1939), Wortis, Bowman *et al.* (1937), O'Neill (1938)], camphor and sympatol [Theato (1939)], strychnine [Molony and Honan (1937), McKendree (1938)], digitalis [Easton (1939), Murphy (1939), Lester (1938–39), O'Neill (1938)], and cardiazol [Lester, (1938–39)], but none appear to have any effect other than that of supporting the circulation.

(c) *Blood-letting.*—Theato (1939) also recommended the withdrawal of 200 c.c. of blood as a means of supporting the circulation. This would probably prove useful in those cases in which signs of pulmonary oedema indicate the onset of right-sided heart failure.

(d) *Blood transfusion.*—This is a valuable means of supporting the circulation, and has already been considered under a previous heading.

(3) *Maintenance of Respiration.*

(a) *Oxygen and carbon dioxide.*—Continuous inhalation of oxygen and 5 per cent. carbon dioxide through a nasal catheter is most useful, and may tide the

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patient over what would otherwise have been a fatal phase. Its use is reported by Gillman and Parfitt (1938), Strecker (1938), Kant (1940) and Finiefs (1938*a*). The use of higher concentrations of carbon dioxide or of a rebreathing bag (Goldman, 1940) is useful in cutting short the myotonic spasms if these have been allowed to develop.

(b) *Respiratory stimulants.*—Lester (1938–39) used lobeline to stimulate the respiration, while a large number of authors have given atropine, e.g. McKendree (1938), Wortis, Bowman *et al.* (1937), Goldman (1940), Cleckley and Templeton (1941) and Proctor and Easton (1944). It is certainly most useful when early signs of pulmonary oedema are developing, and in addition to the effect upon the respiration, it reduces the amount of salivation and so minimizes the loss of fluids from the tissue.

(4) *Administration of Insulin-antagonistic Substances.*

(a) *Adrenaline.*— In the early years of Sakel's treatment adrenaline was given almost as a routine in cases of post-hypoglycaemic coma, because of the fact that if equivalent doses of adrenaline and insulin are given intravenously the fall in the blood sugar which would normally follow the injection of the insulin can be entirely neutralized. Strecker (1938), however, found that the administration of adrenaline in prolonged coma increased the incidence of convulsions, a finding confirmed by Horwitz, Blalock and Harris (1938), while Binzley and Anderson (1938) regard its use as undesirable " as it accelerates the rate of an already overworked heart, and any liver glycogen mobilized will be unnecessary because the blood sugar is already normal or above." Wortis, Bowman *et al.* (1937) found that the colour of a patient improved following the injection of 5 minims of adrenaline, but in general, the results of its use have not justified the risk of inducing further convulsions, and the drug would seem to have no place in the treatment of prolonged coma.

(5) *Lumbar Puncture.*

In view of the fact, noticed in a previous section, that the pressure of the cerebrospinal fluid is normal or only slightly raised in post-hypoglycaemic coma, it would appear that lumbar puncture with withdrawal of C.S.F. would not be helpful in the condition. Katzenelbogen (1939), Kant (1940) and Finiefs (1938) amongst others, however, found that it relieved the patients' restlessness, but Fraser and Sargant (1940) were not convinced of its usefulness.

(6) *Administration of Sedatives.*

Patients who die in prolonged coma do so either from exhaustion with myocardial failure or from an added infection such as pneumonia. The severe, generalized myotonic spasms, so frequently found as part of the syndrome, are extremely exhausting and should be controlled as completely as possible. A number of sedatives, e.g. alcohol intravenously [Abely and Feuillet (1941)], paraldehyde [Lester (1938–39)], morphine [Rossman and Cline (1937–38)], and luminal [Theato (1939)], have been given with a view to allaying the general restlessness, but the short-acting intravenous barbiturates such as sodium

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amytal or hexobarbitone are most valuable in aborting and controlling the severe myotonic spasms. Several authors, e.g. Scherb and Stone (1938), Horwitz, Blalock and Harris (1938) and Wortis and Lambert (1939) refer incidentally to their use, but none lays sufficient emphasis on the vital part they play. Ideally, a patient in prolonged coma should never be allowed to have more than one severe myotonic spasm. An intravenous barbiturate should be given at once. Control of the seizure is immediate, and if 1 gm. of the drug is given slowly so as not to produce anaesthesia no seizure will occur for some time. As soon as the seizures restart further barbiturate should be given, and up to 3 gm. of hexobarbitone may sometimes be required over a period of 8 hours, by which time the myotonic spasms will probably have ceased. That the giving of the barbiturate does not retard the recovery of the cerebral neurones follows from the work of Wortis (1935), who showed that barbituric acid derivatives did not depress the respiratory quotient of brain slices in the Barcroft-Warburg apparatus, i.e. they did not prevent the uptake of oxygen by the brain, so that in prolonged coma they should not prevent the recovering brain cells from utilizing the available oxygen as they become able to do so. Indeed, Hrubetz (1938) and Tyler (1940) have shown that the previous administration of barbiturates can prevent the cerebral damage of hypoglycaemia; they can therefore be given with every confidence in prolonged coma.

(7) *Miscellaneous Adjuncts to Treatment.*

Antipyretic methods such as cold packs and alcoholic sponges have been recommended by O'Neill (1938), and ice enemata and iced water lavage by Goldman (1940). Despite the existing alkalosis, Ribeiro and di Lascio (1939) have given sodium bicarbonate, and also a preparation termed "organo-cardio-renal serum" as well as anti-anaemic liver extract ("campolon"). No benefit appears to have accrued from these measures.

As will be seen from the above account, no specific remedy for prolonged coma is available. Nor is one likely to be found until the precise cause of the condition has been discovered. Until that occurs it is necessary to bear in mind that the adverse effects of hypoglycaemia are systemic in character and are not confined to the nervous system. As Dunner, Ostertag and Thanhauser (1933), Ernstone *et al.* (1935), Jorgensen (1940), Tannenberg (1939) and Terron and Malesani (1939), have shown, other systems, and especially the cardio-vascular system, can be directly damaged by hypoglycaemia. In prolonged coma, therefore, we are probably dealing with a heart which has already been damaged. All that can be attempted is to support the circulation as far as possible, and to lighten the demands made upon it by controlling the restlessness and myotonic spasms by the use of intravenous barbiturates.

XII. Theories of Causation of Post-hypoglycaemic Coma.

The large number of theories which have been advanced to explain the cause of post-hypoglycaemic coma indicates that probably none of them is satisfactory. This is because most of the theories do not deal with the funda-

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mental changes which are found in the condition, but content themselves with the discussion of secondary changes which accompany the more fundamental ones. Attention has been devoted too exclusively to the pathological findings in the brain and insufficient attention has been paid to the changes in the other organs; hence the search for the cause of the condition has tended to be limited to the brain, damage to which results in the symptoms of prolonged coma. It is not enough to say that hyperinsulinism causes irreversible changes in the brain; we have to go on to inquire into the causes and nature of these changes, for the cause may not lie in the cells themselves, but in some other organ or organs which control the metabolism of the cells. That is to say, the search for the cause of prolonged coma must be extended to cover the effects of hypoglycaemia in all the tissues of the body, with particular attention being devoted to the organs which play a part in carbohydrate metabolism. It appears that the following facts have not received the emphasis they deserve:

(1) Irreversible changes occur in the cells from prolonged hypoglycaemia, i.e. they cannot be reversed by restoring the blood-sugar level, we need to know the nature of these changes, for it may be possible to affect them in other ways.

(2) These irreversible changes are not restricted to the brain. They occur also in at least the heart (Tannenberg, 1939), the suprarenals (Jansen and Waaler, 1940), and probably the kidneys (MacKeith and Meyer, 1939).

(3) There is a profound disturbance of the ionic balance of the body. This disturbance may itself result in irreversible changes in the cells (Liebert and Heilbrunn, 1940).

(4) There is an equally profound disturbance of the carbohydrate metabolism in prolonged coma (Proctor and Easton, 1942), and it is noteworthy that the improvement in the patient's condition coincides with the return of the carbohydrate metabolism to normal.

These facts indicate that probably the ultimate cause of the post-hypoglycaemic coma is not to be found in the effect of the hypoglycaemia upon what may be called the "terminal" tissues such as the cerebral neurones and myocardial cells, but in its effect upon other tissues which control the metabolism of the "terminal" tissues. Of especial interest in this connection is the effect of hypoglycaemia on the adrenal cortex, the pituitary gland and the sympathetic nervous system, all of which are known to play a part in the cycle of carbohydrate metabolism.

The various theories which have been advanced to explain post-hypoglycaemic coma will now be briefly reviewed in the light of the above remarks, and therefore, with the proviso that most of them are concerned with changes which accompany prolonged coma rather than with its cause.

(1) *The Vascular Theory.*
(2) *The Anoxic Theory.*
(3) *The Toxic-metabolism Theory.*
(4) *The Oxyachrestic or Aglucic Theory.*

These theories have already been examined in Section VII above.

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(5) *The Autonomic Imbalance Theory.*

A great deal of work has been done on the behaviour of the autonomic nervous system during hypoglycaemia. Parker (1940) holds that both the sympathetic and parasympathetic divisions are stimulated, while Wespi (1938) believes that "the autonomic response to insulin may vary from day to day in one and the same patient." These changes are probably brought about by the action of insulin on the hypothalamus, and if they become too severe, the cells of the hypothalamus undergo irreversible changes which result in prolonged coma.

(6) *The Increased Combustion of Protein Theory.*

Wortis and Lambert (1939) believe that certain of the manifestations of prolonged coma, such as the fever, can be attributed to an increased combustion of protein in the presence of impaired carbohydrate metabolism. It is difficult to see how this can happen in the case of the nervous system, which can use only carbohydrate in its metabolism.

(7) *The Deficiency of Tissue-essentials Theory.*

This holds that the condition is due to a tissue-deficiency of such essential substances in carbohydrate metabolism as vitamin B_1. The fact that patients developing prolonged coma do not apparently suffer from such deficiencies, that prolonged coma may not develop until the patient has already had many normal comas, and the absence of any response to vitamin B when the condition does occur are sufficient evidence against the theory.

Other theories, such as the too rapid increase in dosage, too profound or too prolonged coma, while of undoubted aetiological significance are not true theories as to the *cause* of prolonged coma, and they have already been considered in Subsection VI on aetiology.

Conclusions.

Summing up, it may be said that the cause of post-hypoglycaemic coma remains unknown, and will probably remain so until a great deal more is known about cellular respiration and the effect of hypoglycaemia upon it. All that is known at present are certain aetiological factors which influence the incidence of post-hypoglycaemic coma. These factors are:

(1) That the majority of prolonged comas occur in the first 14 days of treatment.

(2) That the *depth* of coma is important. If the duration of hypoglycaemia is kept constant, the more profound the hypoglycaemia becomes the greater the possibility of prolonged coma developing.

(3) That the *duration* of hypoglycaemia is important. Cases 1 and 2 reported in subsection V prove that even comparatively light stages of hypoglycaemia, if sufficiently prolonged, can result in prolonged coma.

(4) The prevention of prolonged coma is directly related to the skill and experience of the therapist. Post-coma confusion is a warning sign that the patient may develop prolonged coma on the following day, and patients developing such confusion should be given a few days'

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rest from treatment. Patients on hypoglycaemic treatment should be given fully adequate diets, including more than ordinarily sufficient amounts of vitamin B, as a relative deficiency of this vitamin may easily occur. This is the more important, as the increase in weight which usually accompanies the treatment may mask the presence of nutritional deficiencies.

SUMMARY.

This paper deals with the nervous complications of Sakel's treatment. The most important of these is post-hypoglycaemic coma. Two examples of this condition which followed light coma of long duration are described, and the aetiology, pathology, physiology, symptomatology, prognosis, treatment and theories of causation of the condition are discussed.

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