SPONTANEOUS HYPOGLYCAEMIA AND DIABETES MELLITUS ASSOCIATED WITH THE INSULIN COMA THERAPY OF SCHIZOPHRENIA.

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[Received 6 October, 1949.]

THIS paper is concerned with two schizophrenic patients showing unusual complications of Sakel's insulin coma therapy. The first had a series of attacks of spontaneous hypoglycaemia apparently uninfluenced by the temporary withholding of insulin; the other developed diabetes mellitus a short time after finishing his treatment.

This is the first time that either of these complications has been encountered in a series of over 1,000 cases treated by this method at Crichton Royal. Furthermore, neither reference to the literature nor enquiry at other centres with considerable experience of the treatment has revealed any account of similar occurrences in relation to Sakel's insulin coma therapy.

It is hoped that the cases may be of interest not only because of their rarity, but also in relation to the general problem of carbohydrate metabolism and the action of insulin thereon.

CASE 1.—A. K—, aged 23, a house painter by occupation, was admitted to Crichton Royal on 6.iv.48 and diagnosed as a case of paranoid schizophrenia. His main symptoms were delusions of persecution, ideas of reference and occasional auditory hallucinations. He had had a previous attack in 1945 while serving in the Navy. On that occasion he made a good recovery after a course of insulin coma therapy, which passed without incident and he was discharged from the Navy in February, 1946.

During the present illness he showed some insight and voluntarily sought treatment. His personality was well preserved and it was considered that the prognosis for this attack was good and that he would benefit from another course of insulin coma therapy.

Physically he was a well nourished man of athletic habitus, and routine examination did not reveal any abnormality. He commenced treatment on 26.iv.48, and had his first coma with a dose of 200 u. of insulin on 4.v.48. His progress after this was as follows:

5.v.48: Coma on 200 u.

6.v.48: Urticarial rash on abdomen. Only sopor on 200 u.

7.v.48: Rash more widespread. No reaction to 230 u. Benadryl mgm. 100 *t.d.s.* started.

8.v.48: Urticaria improved. No reaction to 250 u. of a different brand of insulin.

9.v.48: Sunday. No treatment. Urticaria greatly improved.

10.v.48: Urticaria cleared. No reaction in the forenoon to 250 u., but at 10.30 p.m. went into sopor. Recovered after 140 ml. of 33 per cent. (w/v) sucrose solution.

11.v.48: Drowsy after 260 u. No sopor or coma and was able to drink 33 per cent. (w/v) sucrose solution.

12.v.48: Went into coma at 1 a.m. Recovered after 570 ml. of 33 per cent. (w/v) sucrose solution by nasal tube. No insulin. Benadryl discontinued.

13.v.48: Forenoon, 30 min. coma after 270 u. After waking he was confused and wept for a while. Later he vomited and was given 100 ml. of 33⅓ per cent. (w/v) glucose solution i.v. Rather tired all afternoon, but otherwise normal.

14.v.48: At 2.10 a.m. went into coma and required nasal feed. Despite this he received 200 u. at the usual time and had a 30 min. coma.

15.v.48: Perspiring profusely at 1.30 a.m. and given 280 ml. 33 per cent. (w/v) sucrose solution. In sopor at 7 a.m. and had to be fed nasally. No insulin.

16.v.48: Signs of hypoglycaemia at 6.30 a.m. Recovered quickly after drinking 850 ml. 33 per cent. (w/v) sucrose solution. No insulin.

17.v.48: Received 180 u. at 7.30 a.m. and went into coma at 8.30 a.m., i.e. about 1½ hours earlier than usual.

18.v.48: 180 u. at 7.30 a.m. In coma at 9.20 a.m. Roused normally. At 10 p.m. he showed signs of hypoglycaemia, which cleared after 280 ml. 33 per cent. sucrose solution. It was decided to discontinue the insulin therapy.

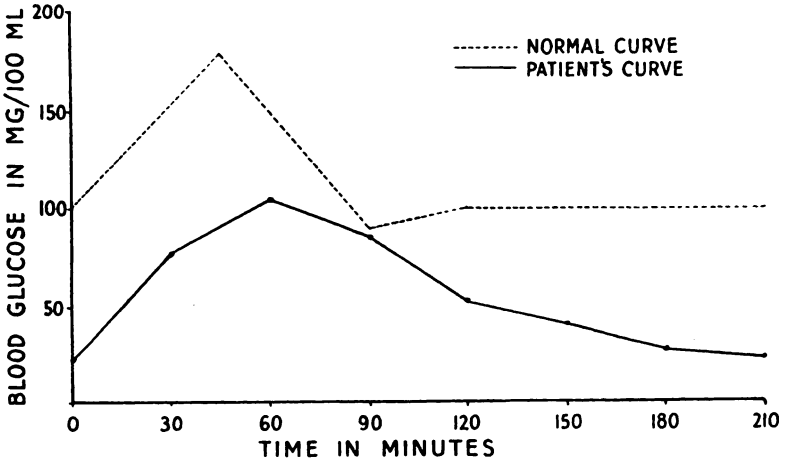

FIG. 1.

19.v.48: In sopor at 5.45 a.m. and recovered after 280 ml. 33 per cent. (w/v) sucrose solution. Although he received no insulin he went into sopor at 8.10 a.m. and was given 100 ml. of 33⅓ per cent. (w/v) glucose solution i.v.

20.v.48: Showed hypoglycaemic symptoms in the morning and at 8.10 a.m. his blood glucose was 21 mgm./100 ml.

21.v.48: Showed gross signs of hypoglycaemia when sent for a glucose tolerance test at about 9 a.m. The fasting blood-sugar level was 16 mgm./100 ml.

22.v.48: Signs of hypoglycaemia in the morning. An extra meal at 10 p.m. was instituted.

23.v.48: No signs of hypoglycaemia.

24.v.48: Glucose tolerance test repeated. Fasting level was 21 mgm./100 ml., but he did not have any clear symptoms of hypoglycaemia (Fig. 1).

During the ensuing couple of weeks various tests were carried out. Insulin sensitivity was found to be normal. In tests of liver function the serum colloidal gold reaction was negative and although the Galactose Index was 195, which is above the generally quoted limit of normality, it was not considered to be significant when considered together with other factors. Urinary diastase was normal and the excretion of 17-ketosteroids was 16.8 mgm. in 24 hours. X-ray of skull was normal.

On three occasions blood was taken for glucose estimations at two-hourly intervals during the day and night. Readings at midnight and 2 a.m. were low on each occasion.

On 7.vi.48 the extra evening meal was dispensed with, as the patient had not shown hypoglycaemic symptoms for some days. Two-hourly estimations on 10–11.vi.48 gave the following blood-glucose readings; no signs of hypoglycaemia were present at any time.

4 p.m.—	86 mgm./100 ml.	4 a.m.—	42 mgm./100 ml.
6 p.m.—	58 ,,	6 a.m.—	58 ,,
8 p.m.—	107 ,,	8 a.m.—	49 ,,
10 p.m.—	63 ,,	10 a.m.—	167 ,,
Midnight—	26 ,,	Noon—	121 ,,
2 a.m.—	23 ,,	2 p.m.—	104 ,,

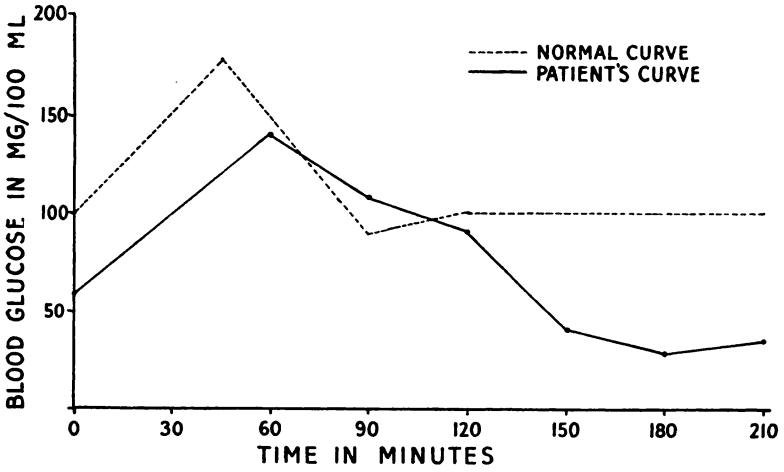

FIG. 2.

Meals were taken at 8 a.m., 1 p.m. and 6 p.m.

As a glucose tolerance test on 12.vi.48 gave a curve (Fig. 2) which appeared to be within normal limits although the readings at 3 hours and 3½ hours were low, it was decided to resume treatment cautiously. On 14.vi.48 a trial dose of 5 u. of insulin was given and on the following day 50 u. On each occasion blood-glucose estimations were made at frequent intervals. As the response was normal, it was considered safe to resume the course of insulin coma therapy. This was completed by 31.vii.48 without further incident, the coma dose being 180 u. A glucose tolerance test which was within normal limits was carried out before his discharge on 4.ix.48 in a state of good remission from his attack of schizophrenia.

Summary.

This schizophrenic patient had a successful course of insulin coma therapy in 1945. Three years later he relapsed and was started on another course. During this he had several attacks of spontaneous hypoglycaemia which continued many days after insulin injections had been discontinued. An urticarial rash occurred before these attacks commenced. Blood-glucose estimations showed a gradual return to normal over a period of four weeks and the course was resumed and completed without further incident.

Comment.

Careful history taking failed to elicit any account of previous attacks which might be construed as due to hypoglycaemia. The patient had never taken

https://doi.org/10.1192/bjp.96.402.285 Published online by Cambridge University Press

particular precautions about his diet and was apparently untroubled either after missing meals or after unduly heavy meals.

At a follow-up interview in May, 1949, he stated that he had not had any hypoglycaemic symptoms since his discharge. He is a good witness and is, of course, very familiar with these symptoms.

The only report of a similar occurrence discovered in the literature is that by Kautzky (1948). His patient was an involutional melancholic of 68 years who had received three courses of modified insulin therapy within a year. The dose had been as high as 110 u., and he had gone into coma on five occasions. A fortnight after the last treatment with insulin he started hypoglycaemic attacks, with blood-sugar levels as low as 20 mgm./100 ml., nightly between 12.30 a.m. and 6 a.m. After a fortnight an extra meal at midnight was introduced and this stopped the attacks. After a further ten days this meal was omitted, but the attacks did not recur up to the time of his death from bronchopneumonia 8 months later. At autopsy changes in the pancreas due either to arteriosclerosis or chronic pancreatitis were found, but were not considered causative.

In trying to find an explanation of the transient spontaneous hypoglycaemic attacks one must bear in mind Conn's (1940) assertion that on a normal diet depression of the fasting blood sugar below 50 mgm./100 ml. indicates an organic cause for the hypoglycaemia with but few exceptions.

Hypofunction of the pituitary and of the adrenal cortex are alleged to be occasionally responsible for spontaneous hypoglycaemia, but neither clinical nor laboratory findings suggested a deficiency in our case. The Galactose Index was rather high, but it was not considered significant, as the other test of liver function were normal and the glucose tolerance curve was not of the high plateau type observed in cases of hepatic insufficiency.

The type of glucose tolerance response called by MacLean (1926) the "lag" curve and by Lawrence (1936) oxyhyperglycaemia, is believed by Hastings-James (1949) to account for most cases of idiopathic spontaneous hypoglycaemia. It did not occur in our case. It is also relevant to note that the patient had not undergone any gastric "short-circuiting" operation; hypoglycaemic symptoms have been noted to occur in patients after this type of operation when the rapid emptying of the stomach produces rapid absorption of glucose and a "lag curve" effect.

A short period of unusual stimulation of the islet cells is the most probable explanation of the recorded series of events.

It is unlikely that the allergic reaction was in any way relevant; similar reactions take place in a proportion of all patients receiving insulin without usually affecting the dosage. It seems possible that there may be some relationship between our observation and the phenomenon whereby insulin dosage can be greatly reduced or even stopped for a while in certain early cases of diabetes which have been treated energetically. This presumably depends either on a sensitization to insulin or on a temporary stimulation of the islets, but, unfortunately, the exact mechanism is not known.

CASE 2.—S. S—, a Jewish youth, aged 18, a pharmaceutical student, was admitted to Crichton Royal on 8.vii.48. He was of leptosomatic habitus, and

routine physical examination did not reveal any abnormality. Urine analysis on admission gave normal results.

Although no member of the family had been in a mental hospital there was evidence of psychotic traits on father's and mother's side. The paternal grandfather was described as " solitary, slovenly, miserly and liable to try to interfere with his daughters and with other women." The patient's mother had short " nervous breakdowns " after the birth of each of her three children. The father was of pyknic habitus and a first cousin of the father developed diabetes at the age of 15 years and died at the age of 19 of pneumonia.

The parents stated that the patient, the first child, was wanted, but that because of her " nervous breakdown " the mother was unable to breast feed him. He was bad tempered and difficult with his food. He developed normally, passing the various milestones at the usual times. He was mischievous, and when very young he used to wander away from home frequently. His parents were both at business during these years and did not spend a great deal of time with him.

The patient's performance at school was very variable. The teachers complained that he day-dreamed and did not make use of his talents. He matriculated at 15 years. He disliked games and was a poor mixer.

His behaviour has given rise to some concern since about the age of 14 years. He became very irritable and quarrelled constantly with his younger sister and brother. When he was about 16 years he brought home a note-book from school and showed it to his parents. It contained a detailed description of another boy who masturbated in school and of the excitement which this induced in himself. This note-book was also a record of the emotions he had experienced since his first day at secondary school, mainly about his sexual interest in other boys. It recounted how he was attracted, disgusted and excited by watching them masturbate.

During the year prior to admission the patient became more withdrawn and suspicious, complaining that his parents were treating him badly and that people were laughing at him. He became dirty in his habits and hid dirty clothes on top of cupboards. Nevertheless, he was apprenticed as a pharmacist and, as far as is known, worked satisfactorily. It appears that he had some insight, as it was at his own request that he was taken to see a psychiatrist.

On admission he was quiet and co-operative, but was soon observed giggling frequently to himself. He spent much of his time striding up and down the ward " practising keeping my back straight." His stream of talk was free and for the most part coherent, but occasionally there was evidence of thought disorder He produced many neologisms but did not use them in conversation. He stated that words kept coming into his head because of his boredom. Examples which he gave were " fillible, rigarallo, sutent, tervinate, imbucibly, susquinaceous." Of the latter he said " It means something less than the nature of a quin. I went to a library and got out a book by a man called Quin: it was on spiritualism, probably a coincidence, really."

Objectively he showed shallow and incongruous affect and he made complaints such as " my emotions have disappeared, I feel dried up inside." He had marked ideas of reference. He described a great number of coincidences in a film which he had recently seen and how they all applied to him.

Symptoms of depersonalization and derealization were prominent. He complained, " I don't know what is me and what isn't. When I look in the mirror my face seems different from before," and again, " There is a certain sense of unreality about everything, everything seems very sharp, my senses are very acute. . . . I have no sense of perspective when I look out of my body."

Intellectual functions tested by Raven's Matrices Test and the Mill Hill Vocabulary test were found to be above average (Grade 2 in both tests). The diagnosis schizophrenia was made and he started a course of insulin coma therapy on 19.vii.48 The course passed without incident except for a break of one week, when he had tonsillitis. He had 53 comas with 7 insulin fits. His coma dose varied between 100 u. and 70 u. Treatment finished on 2.x.48.

The patient showed considerable improvement. He lost his ideas of reference and became more sociable. There was no longer any evidence of thought disorder. The symptom of depersonalization, however, remained and in fact he considered that they were more marked than before. Thyroid was given as Elityran Tablets (Bayer) in progressive doses. During the next few weeks there seemed to be a slow but steady improvement in his mental state. He complained of tiredness,

however, and began to lose weight early in November. This was thought to be due to the Elityran, which was discontinued on 11.xi.48. However, loss of weight continued and polyuria and polydipsia developed. Urine tested on 7.xii.48 gave a strongly positive Benedict's reaction and a positive Rothera's test. The following day a glucose tolerance test was performed which gave a typical diabetic curve with a fasting level of 208 mgm./100 ml. and rising to a peak of 417 mgm./100 ml. at 1½ hours (Fig. 3). Treatment with increasing doses of soluble insulin and a reduction of carbohydrate in the diet was commenced and by 31.xii.48 the diabetes was

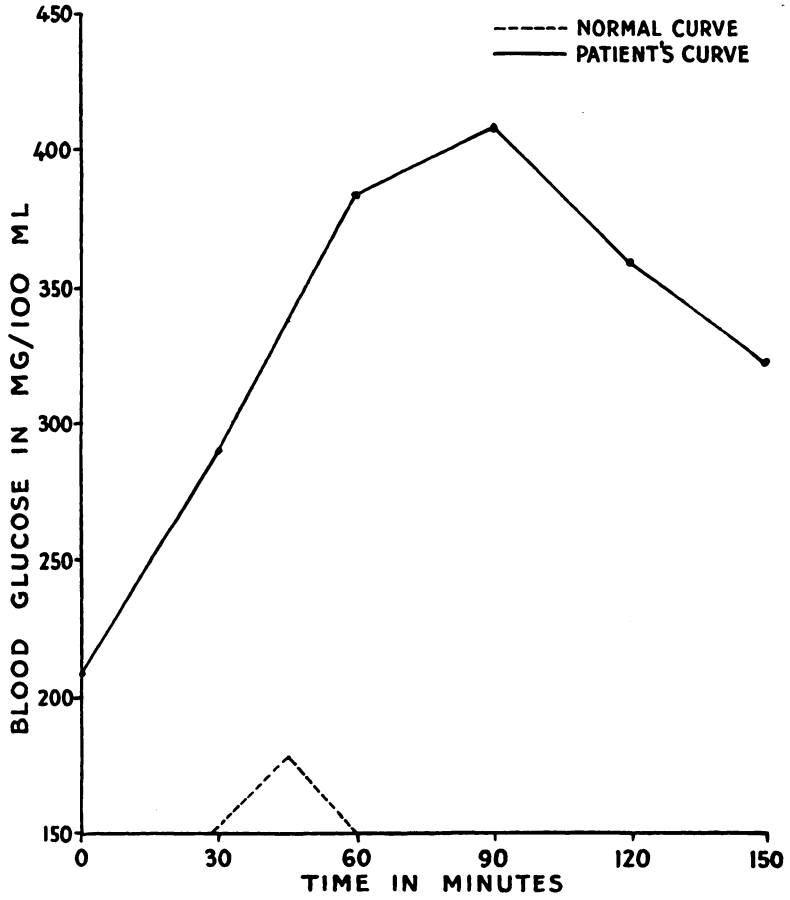

FIG. 3.

controlled with 40 u. morning and 35 u. evening. A change to protamine zinc insulin 50 u. + soluble 20 u. was made on 15.i.49. It was found possible to reduce this dose progressively until by 31.i.49 he was free of symptoms and showed no glycosuria although without insulin. A glucose tolerance curve at this stage did not rise above 190 mgm./100 ml., but showed a delayed return to normal.

The patient was discharged on 15.ii.49, although still experiencing depersonalization phenomena. It was considered reasonable to give him a trial in a different environment, since most of his psychotic features had cleared.

He had to be readmitted on 15.iii.49. His mental state had deteriorated considerably, he was dirty and untidy, giggling incessantly to himself during interviews, although professing to be in a state of great distress. He retained his symptoms of depersonalization and had marked passivity feelings.

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His physical condition had also deteriorated. Urine contained glucose 0·4 gm./100 ml. and Rothera's test was "slightly positive." Fasting blood sugar was 104 mgm./100 ml. and the glucose tolerance curve was frankly diabetic.

Summary.

A Jewish youth developed diabetes mellitus after treatment by insulin coma therapy for a typical attack of hebephrenic schizophrenia characterized by thought disorder, ideas of reference, incongrous affect and symptoms of depersonalization. A first cousin of his father had been a diabetic, presumably also of the early insulin-sensitive type.

Comment.

This case has been described at some length in order to establish firmly the diagnosis of schizophrenia, since reports in the literature give the impression that the occurrence of diabetes mellitus in patients suffering from schizophrenia is remarkably rare. It is, of course, possible that this impression is false and that statistically, it could be shown to be due to chance, as diabetes is relatively uncommon in the age groups when schizophrenia is frequent.

Six cases of true diabetes were found among 279 Jewish schizophrenics by Ligterink and Simons (1936). They reported that all their cases belonged to the pyknic type and all showed an hereditary disposition for manic-depressive psychosis. This they considered to be in keeping with Reiter's (1927) suggested explanation of the rare combination of diabetes and schizophrenia, namely, that "Pyknics develop diabetes mellitus because their habitus predisposes to vegetative kinds of metabolic disorders, whereas leptosomes do not develop diabetes."

The patient described in the present paper was not pyknic, neither could an hereditary disposition to manic-depressive psychosis be shown, although the nature of the mother's recurrent psychosis could not be clarified.

Single cases of the concurrence of diabetes and schizophrenia have been reported, as, for example, by Moellenhoef and Moellenhoef (1942). Their case was diagnosed as a diabetic at the age of 15 and as schizophrenic at 26 years. Kasin and Parker (1943) reported one case; in reviewing the literature they concluded that the only other fully substantiated case previously reported was that of Hofman-Bang (1928). They particularly stress the importance of distinguishing psychotic pictures associated with diabetes itself from true schizophrenia occurring with diabetes.

It is difficult to voice an opinion on the relationship between the insulin coma therapy and the onset of diabetes in the present case. No similar incidence could be found on perusing the large literature on complications during this treatment. It seems that the patient had an hereditary predisposition to diabetes. In view of Harris's (1949) comments on the incidence of cousin marriages among the parents of patients developing the early insulin-sensitive type of diabetes, it may be noted that there was no blood relationship between his parents. Looney and Cameron (1937) have shown a decrease of sugar tolerance for a period after a course of insulin coma therapy and suggested that it was due to a stimulation and sensitization of the adrenal mechanism.

On the other hand, Haist *et al.* (1940) showed that diabetes can be prevented in a dog receiving injections of anterior pituitary extract provided that insulin is given at the same time. They even suggested the prophylactic use of insulin experimentally in families with marked heredity but, of course, not in coma doses.

In the absence of an explanation it is tempting to assume an interference with genetically susceptible hormonal mechanisms, but such an assumption can only be speculative.

Summary.

Two unusual complications of the insulin coma therapy of schizophrenia are reported.

The first patient had attacks of spontaneous hypoglycaemia over a period despite the withholding of insulin. Blood glucose studies are recorded. They showed a gradual return to normal over a period of four weeks.

The second patient developed diabetes mellitus within about a month of completing a course of insulin coma therapy. It is suggested that this patient was genetically predisposed to diabetes mellitus.

Comment is made on the rarity of reports in the literature of the occurrence of schizophrenia and diabetes mellitus in the same patient.

Acknowledgments.

My thanks are due to Dr. P. K. McCowan for permission to report these cases and to Dr. W. Mayer-Gross for his interest and helpful criticisms.

The blood glucose estimations were carried out by Mr. J. W. Walker according to the method of King *et al.* (1937).

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