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A Year's Experience of Insulin Therapy in Schizophrenia¹

By G. W. B. JAMES, RUDOLF FREUDENBERG, and A. TANDY CANNON

WHAT is known as the insulin shock therapy of schizophrenia, introduced by M. Sakel in 1933 at the Pötzl Clinic, Vienna, has been in use at Moorcroft House, Hillingdon, since January 1, 1937. This communication summarizes the experiences of 1937, 24 cases being completed during the period.

The technique of the authors has been described in an article contributed to the *Lancet* (1937), which does not require any essential modification.

Throughout 1937 we have begun treatment at the hour of 7 a.m., and the total hypoglycæmic period has seldom been allowed to exceed five hours. In exceptional cases in which coma has arrived very late we have extended the period up to six hours. This means that interruption usually occurs at the latest at 12 noon, a time convenient for hospital administration, as it allows patients to be bathed and dressed and ready for lunch at the usual hour of 1 p.m.

From experience we believe it to be wise to drop the term "shock", because we feel that in some quarters there is a tendency to magnify the dangers of insulin therapy. Müller (1937) in a series of 495 cases treated in Swiss hospitals, gives the mortality rate as 0.5%, and it is probable that with improvement and standardization in technique this mortality rate may be still further reduced. With proper supervision and immediate access to the appliances necessary to deal with emergencies, very few are really alarming. We return later to this question, but would add here that it is easy to become lulled into a sense of security by the regular passage of days or weeks of treatment without incident. Emergencies come with dramatic suddenness, and fatalities would be certain were there any relaxation in vigilance or lack of essential appliances.

The brand of insulin has been varied. For the first six months we used a brand of pure crystalline insulin, changing at the end of this period to a gland extract. There has been no urticaria in the whole of our series, and no differences were observed in the effects of the two preparations.

Dosage.—Even after a year it is not easy to give any precise information about the average dosage of insulin required to produce hypoglycæmic coma. We aim at producing coma in the third hour of hypoglycæmia. Coma has been produced by 15 units, while another case required over 400 units. This wide variability in sensitivity to insulin is very striking, and dosage cannot be forecast with any accuracy. Insulin tolerance appears to vary in the same patient during the course of treatment, some patients developing an increased resistance, others an increased sensitivity. In the great majority of our cases, dosage has been decreased after the initial coma dose has been reached. For example, if the initial coma dose is found to be 100 units, that dose may be reduced to 90, 80, or even 70, units later in the treatment, to produce satisfactory coma. We agree with Müller (1937) that this variability in sensitivity bears no relation to mental improvement or the reverse.

Effect of dosage on blood-sugar.—Blood-sugar estimations that have been made show a fairly constant series of changes. Within an hour of the injection the blood-sugar falls to 30 mgm. per 100 c.c., or even less. It remains at about that level during the whole of the hypoglycæmic period. Half an hour after interruption, when

¹ A film was demonstrated at the meeting, divided into two parts; the first, showing the normal course of insulin therapy from injection to interruption in the same patient, the second consisting of "shots" of different patients showing the phenomena of hypoglycæmia.

the patient is conscious, the blood-sugar has risen to a little below normal; about one hour after interruption it has returned to normal, and continues to rise under the influence of the large carbohydrate supply.

The order of appearance of neurological and psychological effects of hypoglycæmia.—This subject has been carefully described and considered by Parfitt (1937), and our daily records in the main confirm his observations. Parfitt (1937) has stated that he saw no improvement as a result of insulin fits. Our observations on this point show that four patients whose symptoms had lasted up to eighteen months before admission definitely dated mental improvement from the occurrence of a single insulin epileptiform attack. We were so impressed by these observations that we used cardiazol in certain cases in addition to insulin, to induce epileptiform seizures. The cardiazol is now given one to two hours after the injection of the coma dose (Georgi, 1937). A small group of cases cannot justify the drawing of conclusions, but references are made to results in Table II. The criticism may, very properly, be made that it is impossible to know whether improvement has been due to insulin or cardiazol, as so many patients in our small series have had both. We continue to use insulin and cardiazol combined in selected cases, and incline to the view that the combination of the two methods may show better therapeutic results than either alone.

The duration of coma.—It is very essential that the daily length of coma be extended gradually, and not allowed to continue beyond a period at which the patient is found by experience to rouse easily after interruption and to remain free from after-effects. In any case deep coma should never be extended beyond a period of one and a half hours (Dussik and Sakel, 1936). This optimum length of coma depends chiefly on physical reasons; some patients seem built to stand lengthy comas which others are unable to tolerate.

The interruption of hypoglycæmia.—In our communication on the technique of insulin therapy (1937) we described the precautionary passing of the nasal tube when severe muscular twitchings, for example, suggested the imminence of an epileptiform fit. We have learned to drop this procedure, and if an epileptiform attack does develop we no longer interrupt intravenously, but pass the tube at the conclusion of the first fit, apparently with perfect safety. In our 24 cases we have had 73 epileptiform attacks due to hypoglycæmia; 14 of them were interrupted intravenously, and 59 by tube. We no longer regard an epileptiform attack as an emergency, and we mention this fact here as it modifies our former published view.

Intravenous interruption.—During 1937, with a total of 1,628 patient-insulin days, intravenous interruption was necessary on 106 occasions. Table I summarizes the reasons for intravenous glucose therapy. This total of 106 does not include the 14 occasions on which intravenous glucose was used to interrupt epileptiform attacks. Nor does it include those occasions on which intravenous glucose was necessary in the afternoon or evening. The table refers exclusively to intravenous interruption necessary during the period of morning comas, and tabulates the reasons for its use.

In this table there is an apparent contradiction to what has been said before regarding the interruption of epileptiform convulsions, in that two patients (Cases 17 and 18) were interrupted intravenously when epileptiform fits threatened. Both these patients were adversely affected mentally by fits, and often vomited and refused food. Premedication by luminal was tried unsuccessfully in both cases.

In the course of 1937, two serious emergencies with danger to life occurred. The first was in a male aged 34 with a paranoid schizophrenic history of eleven years. He was of the thin asthenic type. There was also a history of previous cardiac collapses, and his treatment was undertaken with reluctance. Twenty-eight comas were given without serious incident, except that irregularity of the pulse was frequent, and was accompanied at times by cyanosis. The twenty-ninth coma was induced by 70

units, the same dose as on the preceding days. At 10.5 a.m. an epileptiform attack occurred, followed by an unusual pallor. The patient suddenly became pulseless, and his veins were so collapsed that intravenous glucose proved impossible. 0.5 c.c. adrenaline 1 : 1,000 was given subcutaneously, followed at once by 2 c.c. of 33½% glucose intracardially. Restoration was immediate, and intravenous glucose possible. There were no subsequent ill-effects, but in view of the chronic nature of the psychosis, cessation of the treatment was decided upon.

TABLE I.—REASONS FOR INTRAVENOUS INJECTION OF 33% GLUCOSE.

No. of case	Total insulin days	Failure to arouse 30 minutes after tube feed	Epileptic attack after interruption by tube	Introduction of nasal tube impossible	To avoid threatened epileptic fit. Severe myoclonic twitchings	Laryngo-spasm	Cardio-vascular reasons	Vomiting of feed		
		<i>a</i>	<i>b</i>							
1	64						1			
2	35	1						2		
3	56	3	1*							
4	44	2								
5	45					1				
6	71	10								
7	39	1	1					1		
8	94			1		1				
9	78	3				1		6		
10	64			4						
11	82	2				1				
12	118	3								
13	26	1								
14	71	1						3		
15	79	11								
16	78									
17	92	8		1	10					
18	78	3		1	1					
19	72	7					1			
20	58	1								
21	67					1	1*			
22	61	1								
23	87	6					2			
24	69									
	1,628	64	2	3	4	11	5	5	12	Total 106

a = In this column patients were roused immediately with intravenous glucose, and showed hypoglycæmia.

b = In this column patients exhibited delayed awakening accompanied by hyperglycæmia. Emergencies marked * are described in detail because of their severity.

We quote the second of our two dangerous emergencies in some detail on account of the lessons we believe can be learned from its consideration, and the wide fields of speculation it opens. It occurred in a male, a recent paranoid schizophrenic, aged 24. His physical condition was excellent, but no improvement in his mental state had taken place after 29 comas, and it was decided to extend gradually the length of coma. His thirtieth coma was induced by 130 units. He became unconscious at 9 a.m. ; at 10.45 the corneal and plantar reflexes disappeared, and the patient was hypotonic. He was allowed to remain in this deep coma until 11.20, when interruption took place. No anxiety was felt about the patient, but at 11.50 he was not awake ; restless motor movements, with opisthotonus, and flushed face, were noted. On examination the corneal reflexes were again present, but the plantar responses were both extensor. The pulse-rate rose to 140 and the blood-sugar was 230 mgm. per 100 c.c. at this time. This estimation was not known when 100 c.c. of glucose were given intravenously in the belief that the above symptoms were due to hypoglycæmia. No further glucose was given. This case emphasizes what is seen in Table I. If hypoglycæmia persists after the tube feed, a waking after intravenous glucose is certain and immediate.

The difficult cases are those in which coma persists in spite of hyperglycæmia (Freudenberg, 1937).

12.45 p.m. : No change ; 2 c.c. (1,000 units) of vitamin B₁ (Roche) and 8 c.c. calcium chloride solution (0.8 grm.) were given intravenously, the former for its effect on sugar utilization (Freudenberg, 1937), the latter to counteract the alkalosis known to exist in such conditions.

1.30 p.m. : Condition unchanged ; blood-sugar 235 mgm. per 100 c.c. 2 c.c. (1,000 units) of vitamin B₁ (Roche) given intramuscularly.

1.50 p.m. : Lumbar puncture carried out, and 15–20 c.c. of clear fluid under pressure removed. The sugar in the cerebrospinal fluid stood at 300 mgm. per 100 c.c., comparing very nearly with a similar case quoted by Molony and Honan (1937).

2.20 p.m. : Blood-sugar 180 mgm. per 100 c.c. Pulse 120.

2.40 p.m. : Semiconscious and answering vaguely. Perseveration present. Reflexes normal.

4 p.m. : Blood-sugar 100 mgm.%, pulse 108. Drank some tea.

5.30 p.m. : Temperature 101° F.

During the next three days the patient slowly improved, but vomiting, headache, and somnolence with restless intervals were present. On the fourth day he began to talk, and on the sixth day showed a return of insight and disappearance of paranoid ideas. He made an uninterrupted recovery and has resumed his work. Later experience outside the series under review has taught us that a blood transfusion would have been of the utmost value as an aid to restoration.

We learnt from this case that to prolong deep coma up to so long a period as one and a half hours may be followed by difficulty in restoring the patient. On the other hand the excellent therapeutic result obtained surely shows that prolonged deep coma may be necessary in certain cases, in spite of its added risk.

Late hypoglycæmia.—Among the 1,628 patient-insulin days, there were 18 occasions on which hypoglycæmic symptoms returned in the afternoon or evening. They were all due to insufficient meals, or vomiting during the day, and careful instruction of the nursing staff on the necessity for adequate meals has reduced such events to a minimum. They were dealt with by the introduction of glucose either by mouth, by tube, or intravenously.

CLASSIFICATION OF RESULTS

We urge the adoption of some standard method of classifying results. Our own series is classified strictly on the lines suggested by Müller (1936), which are as follows :—

(1) *Complete remission.*—This category represents complete disappearance of schizophrenic symptoms, with normal affective relationship, full insight, and ability to return to the normal sphere of work.

(2) *Incomplete remission.*—This category includes patients who are able to work but with persistence of any one of the psychic symptoms described under (1).

(3) *Partial remission.*—Patients in this category are able to resume work ; but symptoms remain without interfering with their daily life.

(4) *Unimproved*, and requiring hospital care.

It has seemed to us wise to classify our own results on Müller's categories, for the sake of comparing our figures with published Swiss results.

Experience of these categories has shown us many difficulties in accepting them entirely, difficulties that we believe are shared by other workers.

Table II summarizes our results.

TABLE II.

No.	Diagnosis	Results					Insulin days	Comas	Insulin fits	Cardiazol fits	Total dose (units)	Average daily dose	
		+++	++	+	0	*							
<i>Cases under 6 months</i>													
1	Catat.	+++					64	39	1	0	1,351	21.1	
2	Paran.	+++					35	21	0	0	3,025	84.4	
3	Paran.		++				56	30	1	3	5,980	106.7	
4	Paran.	+++					44	32	0	0	4,705	109.0	
5	Cat. stu.	+++					45	19	1	3	8,382	186.2	
<i>Cases from 6-12 months</i>													
6	Cat. stu.		++				71	53	0	3	6,185	87.0	
7	Cat. stu.		++				39	11	0	1	5,685	145.9	
<i>Cases from 12-18 months</i>													
8	Cat. stu.		++				94	7	1	9	10,200	108.5	
9	Paraphr.				0		78	63	0	0	6,047	77.5	
10	Catat.		++				64	24	1	0	7,495	117.0	
<i>Cases over 18 months</i>													
11	Cat. stu. (3 years)		++			*	82	59	0	5	17,395	212.0	
12	Catat. (7 ,,)				+	*	118	45	0	0	15,674	132.8	
13	Paran. (12 ,,)		++			*	26	15	3	0	1,570	60.4	
14	Paran. (5 ,,)				0		71	55	0	3	9,720	137.9	
15	Paran. (2 ,,)				0		79	47	2	0	10,050	127.0	
16	Paraphr. (2.3 ,,)				0		78	37	24	0	10,910	138.5	
17	Hebephr. (3 ,,)				0		92	41	5	0	11,460	124.5	
18	Cat. stu. (3 ,,)				0		78	31	7	2	5,360	68.9	
19	Cat. stu. (7 ,,)				0		72	39	0	4	6,435	89.3	
20	Cat. stu. (8 ,,)				0		58	11	1	21	5,260	107.9	
21	Paran. (11 ,,)				0		67	27	1	0	2,590	38.6	
22	Cat. stu. (12 ,,)				0		61	33	2	23	7,015	115.0	
23	Hebephr. (2 ,,)				0		87	57	1	0	4,855	55.9	
24	Hebephr. (2 ,,)				0		69	42	22	0	4,805	69.6	
Totals			4	7	1	12	3	1,628	838	73	77	172,164	2521.6

+++ = Complete remission. ++ = Incomplete remission. + = Partial remission.
0 = Unimproved. * = Tendency to remission.

Cases improved with insulin and cardiazol fits are underlined.

The table demonstrates that out of a total of 10 cases (the total of the first three groups) with symptoms lasting up to eighteen months, nine have returned home and resumed their former occupations. Of the 14 long-standing cases treated, only three show remissions; two have returned home, the third awaits his discharge. It is of interest to note that these three older cases have previously shown a tendency to remission. Some of the old-standing cases treated showed clinical improvement.

Our longest period of treatment is one hundred and eighteen days, our shortest twenty-six days. The average, 67.8. The average total in-patient stay by each patient is about seventy-eight days, a remarkable figure when compared with the time spent in hospital by spontaneous remissions in recent cases, given as two hundred and two days by Dussik (1936). The patient who had treatment only twenty-six days made a rapid recovery, and after a fortnight's probation was allowed to return home, where she remains in very good health, managing a new house. The duration of treatment presents problems at times. Müller (1937) pointed out that insufficient length of treatment produced less satisfactory results. Therefore we have tried to follow his suggestion that at least sixty insulin-days elapse before treatment is abandoned as unlikely to be successful.

Comparing the two broad groups of cases shown in the table—up to eighteen months' duration and over eighteen months—there are several points of interest to be observed. It looks from the table as if the older cases used more insulin for the hypoglycaemic effects, but after calculating the average daily dose for each group we find that the average for the recent cases is 104.5 units, and that for the older group

105.6 units. Again, taking these two broad groups, we find that the percentage of insulin fits per hundred insulin-days is 1.67% in the recent group, and 6.54% in the old-standing group, a fact of interest in relation to the physiopathology of schizophrenia. These percentages closely correspond with the figures given by Plattner and Frölicher (1937).

RESULTS COLLECTED BY THE BRITISH PSYCHIATRIC INSULIN SOCIETY

By the kindness and courtesy of members of the British Psychiatric Insulin Society we are able to present a summary of a further 94 cases which, added to our own 24, make a grand total of 118, out of which number one patient died. The figures have been given to us by Dr. Finiefs, of the Three Counties Hospital; Dr. Hunter Gillies of the West Ham Hospital; Dr. Hamilton of the Bethlem Royal Hospital; Dr. Larkin of West Ham Hospital; Dr. Russell of St. Bernard's Hospital; Drs. Siegheim and Grace Watson, whose work has been done at Millbrook House.

To these generous colleagues and to their Superintendents we tender our grateful thanks. By their kindness we are enabled to give to this Section a table of results which would have taken any one of us alone some years to collect. Cardiazol combined with insulin has been used by most of our colleagues.

TABLE III.

Duration of symptoms	No. of cases	Complete and social remissions		Unimproved
		Cases	%	
Cases under 6 months ...	22	19	—	3
Cases from 6-12 months ...	18	15	—	3
Cases from 12-18 months ...	9	5	—	4
Cases over 18 months ...	69	22	—	47
Total	118	61	51.7	57

Average duration of insulin treatment = 61.4 days.

In Table III we have not adhered to Müller's categories, but summarize results in one column as "complete and social remissions", thus grouping together Müller's "complete, incomplete, and partial, remissions". Further, we do not think that the small numbers in each group of cases justify the use of percentages. We have therefore shown the total percentage only of all groups treated, from those of less than six months' duration up to those of long standing, even up to twelve years. The joint percentage of complete and social remissions works out at 51.7%, which may be compared with a table quoted by Müller (1937), and compiled from 381 Swiss cases treated for a sufficient period. His figure is 52.5%. It is worth noting that in this table of our united cases, in those groups in which the psychosis had lasted up to eighteen months, a total of 49, only 10 remained unimproved, or, put another way, 39 out of 49 recent cases are at home and working.

We submit that if generous allowances be made for differences in diagnosis and estimation of results, these figures are still ahead of spontaneous remissions (30-40%) and other methods of treatment. It remains to be seen how durable these remissions will prove.

SUMMARY AND CONCLUSIONS

We have surveyed briefly the experience gained in a year's insulin therapy at Moorcroft House; reference has been made to certain points of technique, and 24 completed cases have been reviewed.

There have been no fatalities, and but two serious emergencies in 1,628 patient insulin days. The combined use of cardiazol and insulin has been mentioned, but limited experience makes it impossible to decide whether insulin alone, cardiazol alone, or the combined methods will ultimately prove most effective.

Results, and details of interest, have been tabulated. The combined results of work at Moorcroft House and other hospitals have been collected and are appended, making a total of 118 completed cases with one fatality.

The clinical results in recent cases appear to be very satisfactory, and the great reduction of the period of residence in hospital cannot be overlooked.

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