RELATIONSHIP BETWEEN INSULIN COMA THRESHOLD OF SCHIZOPHRENIC PATIENTS AND THEIR RESTING E.E.Gs.

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THE E.E.Gs. of schizophrenic patients have been studied by a number of workers, notably Davis and Davis (1939[1]). P. Davis (1939[1], 1940[2], 1942[3]) attempted a classification of schizophrenic records, defining the main types of pattern. Gibbs *et al.* (1938[4]), Jasper *et al.* (1939[5]), and, more recently, Hill (1946[6]), have noted the presence of epileptic activity in the E.E.G.s of catatonic schizophrenics.

Hill (1947[7]) has studied the changes in the E.E.Gs. of schizophrenics following the injection of insulin. More recently (1951[8]) he has postulated a central homeostatic mechanism acting in normal subjects during induced hypoglycaemia; and has shown that the homeostatic reactions of schizophrenic patients are different and would appear to be defective.

Hoagland, Rubin and Cameron (1937[9], 1938[10]) and Himwich, Frostig *et al.* (1939[11]) have studied the changes in the E.E.G. of patients undergoing insulin comas during and after treatment.

The present paper records an attempt to relate the characters of the resting E.E.Gs. of schizophrenic patients with their sensitivity to insulin, as demonstrated in the dose of insulin required to produce hypoglycaemic coma. As is well known the coma dose of insulin varies enormously in different patients. The E.E.G. of insulin "sensitive" patients have been found to differ, in several respects, from the records of insulin "resistant" schizophrenics.

MATERIAL AND METHOD.

The E.E.Gs. were studied in 54 adult schizophrenics, 37 male and 17 female, at St. Ebba's Hospital. Their records were, for the most part, made while they were waiting to have a course of comas. In a minority of cases the E.E.G. was recorded after the comas had been completed, but at least three months were allowed to elapse after the end of the treatment before the records were made. At the end of such a period the record can be expected to have returned to its pre-treatment form.

The coma dose of insulin was considered to be the number of units required to produce the first coma. The patients were treated under uniform conditions, dietary and otherwise, during treatment and standard criteria for diagnosing "coma" were employed. The patients were considered to be in

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hypoglycaemic coma when they were completely unconscious, when they made no purposive response to painful stimuli, and when bilateral Babinski responses were obtained. In most cases the corneal reflexes were absent.

A six-channel Ediswan E.E.G. was used and with 43 patients full-length recordings were obtained, in the course of which the pens were actually writing for 15–18 minutes. With these records conventional electrode positions were used. In the case of 11 patients whose condition rendered prolonged recordings impossible, shorter records were made using 15 electrodes. In all but 2 cases overbreathing was attempted. Most of the patients had been fasting overnight, i.e., for 15–18 hours. The period of fasting was never less than 6 hours. The records were analysed in the usual visual manner, no automatic waveform analyser being available. For brevity the initials "C.D.I." have been used for the phrase "coma dose of insulin."

E.E.G. Characters Studied.

The following characters were considered against C.D.I.:

1. Alpha frequency of the resting record.
2. Presence or absence in the records of "theta activity" (activity at 4–7 c/s).
3. The presence of fast activity in the records.
4. The presence of paroxysmal activity in the records.
5. The "normality" or "abnormality" of the records.
6. The overbreathing responses.
7. The C.D.I. was also considered against the following factors:
   - (*a*) Sex differences.
   - (*b*) Age of patients.
   - (*c*) Duration of illness.
   - (*d*) Weight and body-type of patients.

Results.

1. *Relationship of Coma Dose of Insulin (C.D.I.) to Alpha Frequency of the Resting E.E.G.*

Table I.

Alpha frequency (cycles per sec.).	Number of cases.	Average C.D.I. (in units).
Under 9 c/s	6	155
9–10 c/s	14	199
10–11 ,,	26	197
11–12 ,,	4	262
12 + c/s	3	60
No countable alpha	1	340

(*N.B.*—Results given here, as elsewhere, to nearest whole number.)

From these figures it appears that insulin sensitivity is not statistically related to alpha frequency. It is worth noting, however, that where the

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alpha activity is slow (under 9 c/s) or fast (above 12 c/s) in our series of cases there is greater sensitivity to insulin. For frequencies within the 9–12 c/s range there appears to be no definite relationship between alpha frequency and insulin sensitivity.

2. *Theta Activity—the Presence or Absence in the Records of Activity at 4–7 c/s.*

The findings are set out in Table II. The "doubtful theta" group includes those records where only traces of slower rhythm were present. It will be noted that the grouping in Table II does not take into account the presence or absence of fast or paroxysmal activity, nor is the normality or abnormality of the records considered.

TABLE II.—*Theta Activity.*

Theta.	Number of cases.	Average C.D.I. (units).
Group (*a*) definitely present . .	30	155
Group (*b*) doubtfully present . .	5	222½
Group (*c*) definitely absent . .	19	243

Comparing cases where theta activity is markedly prominent, we find that such records are associated with a greater degree of sensitivity than is shown by the whole theta group (Table III, below).

TABLE III.

	Number of cases.	Average C.D.I. (units).
Theta prominent . . .	8	123
Theta present but not prominent	22	167
Total	30	155

These figures suggest that patients whose resting E.E.Gs. contain theta activity are likely to require smaller doses of insulin for their comas as compared with patients whose E.E.Gs. contain no theta rhythm. Taking groups (*a*) and (*c*) in Table II and comparing the mean coma levels by the *t*-students method for comparison of means, we find that the difference in the C.D.I.'s is statistically significant (p = less than ·01). See also section 7 (b) below.

A most important point must now be considered; namely, the relation of age with the presence in the records of theta activity. It will be shown in section 7 (b) below that the theta minus group remains fairly constant in respect of insulin coma threshold; the theta plus patients under 21 years are much more insulin resistant than are the theta plus patients of 21 years and over. The theta plus group of patients over 21 years have an average coma dose of insulin of 131 units, as against the average dose for the theta minus group of patients over 21 of 241 units. The difference is 110 units—an even greater difference than when the records of under 21 years are included in the total, and is also a significant difference.

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3. *The Presence of Fast Activity in the Records.*

TABLE IV.—*Fast Activity.*

Fast activity.	Number of patients.	Average C.D.I. (units).
(*a*) Fast activity present and prominent	14	196
(*b*) Fast activity absent or only occasionally seen	40	191
(*c*) Fast activity and theta activity in same record	12	172
(*d*) Fast activity absent and theta activity present	18	144

The above table suggests that on the whole the presence of fast activity in a patient's E.E.G. is not significantly related to his sensitivity to insulin. In records containing slower rhythms, the presence of fast activity may be related to greater insulin resistance but not significantly so.

4. *Paroxysmal Activity.*

Seven of the records contained low voltage "spikes" of the type described by Jasper[5] and Hill[6]. These records showed other evidences of paroxysmal dysrhythmia, and in every instance theta activity was also a feature.

TABLE V.—*Presence of Paroxysmal Activity in the Record.*

Type of record.	Number of patients.	Average C.D.I. (units).
Paroxysmal activity (containing theta)	7	151½
Whole "theta present" group	30	155

There is thus no reason to suppose that the presence of paroxysmal activity *per se*. has any relationship to the coma threshold.

5. *"Normality" or "Abnormality" of the Records.*

It is often very difficult to decide when the records of schizophrenics are abnormal. Their E.E.Gs. are frequently marred by artifacts, and in recent acute cases of the type that provides the majority of our subjects the records are frequently modified by the patients' state of tension.

Of our 54 cases, 6 records were considered to be doubtfully "normal" or doubtfully "abnormal." They will not be considered further. We considered that 28 records were undeniably normal and that 20 records were abnormal.

The types of abnormality encountered were (i) "paroxysmal" records and (ii) "non-specific dysrhythmic" E.E.Gs.; i.e., records containing a mixture of fast and slow activity; (iii) records containing an excess of theta rhythms with little or no fast activity.

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TABLE VI.—*Relation between Normality and Abnormality of the Record and Insulin Coma Dosage.*

Type of record.	Number of patients.	Average C.D.I. (units).
(*a*) Definitely normal	28	225
(*b*) Definitely abnormal	20	153½
(i) Fast-slow dysrhythmic	5	170
(ii) Slow rhythms with little fast	8	145
(iii) Paroxysmal or epileptic activity	7	151½

The difference between the "normal" and "abnormal" groups is considerable as regards sensitivity to insulin. Comparing the mean insulin levels of patients in the two groups we find the difference in coma doses of insulin to be significant (p = less than 0·01).

Thus there is not much difference between the types of abnormality encountered in relation to their insulin sensitivity.

6. *Effect of Overbreathing.*

TABLE VII.—*Overbreathing Responses.*

Response to overbreathing.	Number of patients.	Average C.D.I. (units).
Increased instability	17	153
No appreciable change	35	212

It was impossible to obtain the co-operation of two patients in overbreathing.

The E.E.Gs. of insulin resistant patients tend to be more stable on overbreathing than do those of more insulin sensitive patients.

7. *Factors which might Affect the Coma Threshold.*

(a) *Sex differences.*—The average coma dose of insulin of 37 male patients was 195 units, and of 17 female patients was 186 units. No significant differences were observed between the sexes whenever numbers permitted a comparison.

(b) *Age.*—The relation between age and coma dose may be seen from the following table:

TABLE VIII.

Age.	Number of patients.	Average C.D.I. (units).
18–20 years	11	254
21–25 ,,	21	190
26–30 ,,	10	187
31–39 ,,	8	171
40 + ,,	4	90

At a first glance there appears to be some relationship between age and coma dose. Table IX, however, shows the distribution of theta plus and

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theta minus records in the respective age-groups. Doubtful cases have been omitted.

TABLE IX.—*Relation between Age and Presence of Theta in the Records (doubtful cases omitted).*

Age group.	Theta activity, plus or minus.	Number of patients.	Average C.D.I. (units).
18–21 incl.	—	2	260
	+	8	244
21–25 ,,	—	9	237½
	+	10	125
26–30 ,,	—	5	228
	+	5	146
31–39 ,,	—	3	247
	+	4	130
40	—	0	·0
	+	3	73

These figures show that on the whole there is little variation with age in the coma dose requirements for patients whose records contain no theta activity. The 3 patients over 40 years had all grossly abnormal E.E.Gs. and were remarkably sensitive to insulin.

The theta plus records of the juvenile group (under 21) showed much greater insulin resistance than did those of the group 21–40 years. Omitting the 40 plus age-group we find that, as previously mentioned, of the patients aged 21–40 years, those whose E.E.Gs. contained theta activity had an average coma dose of 131 units, while those without theta activity had an average C.D.I. of 241 units.

(c) *Duration of illness.*—We have arbitrarily taken 18 months from the beginning of illness as the dividing-line between " recent " and " long-standing " cases. To avoid misleading results, we have felt it preferable to confine our attention to the 39 patients in the 21–40 years age-group. We have been able to determine with reasonable accuracy the time of onset of 29 of these patients.

TABLE X.—*Duration of Illness 21–40 Group.*

Duration of illness.	Average age.	Number of patients.	Average C.D.I. (units).
" Recent " cases	27 yrs. 8 months	18	198
" Long-standing " cases	27 ,, 9 ,,	11	150

(d) *Weight and body type.*—Assuming that theta activity has the most striking relationship to insulin sensitivity, we compared the weights of the " theta present " group of patients with the weights of the " theta absent " group.

Male patients :	Average weight of	theta +	group,	9 st. 13 lb.
	,, ,,	theta —	,,	10 ,, 1 ,,
Female ,, :	,, ,,	theta +	,,	9 ,, 2 ,,
	,, ,,	theta —	,,	9 ,, 3 ,,

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Thus the weight *per se* is not related to presence or absence of theta activity in the records.

TABLE XI.—*Body Type: Relation between Body Type and Sensitivity to Insulin.*

Type.	Number of patients.	Theta present or absent.	Average C.D.I. (units).
Asthenic (male)	8	Theta +6 rcds. −2 ,,	162½
Pyknic and near pyknic (male)	7	Theta +2 rcds. −5 ,,	246

It would appear probable that insulin is related to body type as opposed to body weight. It is interesting to note that theta activity was related closely to asthenic build in these cases, but the numbers appear too small to provide anything other than an interesting observation.

We were unable to provide similar comparison between asthenic and pyknic female patients as the numbers involved would have been even smaller.

SUMMARY AND DISCUSSION.

The most significant results from this study were: (1) that taking the group of patients as a whole, those whose E.E.Gs. contained theta activity had comas on smaller doses of insulin than did those whose E.E.Gs. did not contain theta activity; (2) similarly, that patients with abnormal E.E.G. were more insulin sensitive than those with normal records, though the type of abnormality was of much less importance; (3) patients whose E.E.Gs. remained stable on overbreathing were more insulin resistant than were patients whose E.E.Gs. were unstable.

It is interesting to note that sex and weight were unimportant considerations, though the asthenic body-type, at least in male patients, appeared to be related to the presence of theta activity and to greater insulin sensitivity. This is a point which needs further study.

In patients over 21 years, age appeared to be of comparatively little significance in relation to insulin sensitivity, but in the young adult group (under 21) there was less sensitivity to insulin whether theta was or was not present. In fact, the difference between the theta plus and theta minus categories under 21 years was not significant. It is possible that some of the theta plus cases in this group come under the heading of what might be termed "normal immaturity," and, in fact, that these cases tend to behave more like mature adult records in relation to insulin sensitivity, i.e., show a comparatively high degree of resistance.

It is in patients over 21 years that the presence of theta activity in the E.E.G. has significance for insulin sensitivity. Such theta activity could represent immaturity; or some constitutional peculiarity (e.g., where it is combined with paroxysmal activity); or it might result from an acquired disorder of the brain. Perhaps in different E.E.Gs. theta has a different

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significance. That theta activity occurs in a large proportion of the records of schizophrenics is not necessarily true of the older or more chronic patients, although in the patients studied there appeared to be little falling off with age proportionately in the incidence of cases showing theta activity.

Whatever the cause of the theta activity in adult schizophrenics, it suggests a disturbance in the integration of function between the cortex and basal structures. This disturbance may be due to a failure of development of normal cortico-basal interaction with resulting incomplete cortical dominance; or it may be due to acquired impairment of such interaction; or it may be due to abnormal functioning, e.g., the "tendency to convulse."

Davis (1943[12]) and later Hill (1947[7]) induced hypoglycaemia in a number of subjects and found that, where slow rhythms were present in the resting records, the E.E.Gs. during hypoglycaemia showed marked slowing at relatively high blood-sugar levels, i.e., that cerebral function, as shown by the E.E.G., was more vulnerable to changes in environment than was the case when no slow rhythms were present in the resting records. It is interesting to note that Hill *et al.* (1951[8]) has shown that homeostatic reactions to hypoglycaemia in schizophrenics are also defective and differ from those of normal subjects; their reactions to stress are imperfect, and it would appear that these reactions are also more vulnerable. It may be that the presence of theta activity in the more insulin sensitive group of our patients' E.E.Gs. is related to markedly defective homeostatic mechanisms which would render those subjects less able to resist the effects of insulin.

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