THE EFFECT OF INSULIN COMA AND E.C.T. ON THE SHORT-TERM PROGNOSIS OF SCHIZOPHRENIA

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Insulin coma and convulsion therapy have been used very widely throughout the world for the treatment of schizophrenia since their introduction by Sakel (1935) in 1935 and Meduna (1935) in 1934 respectively. Many thousands of patients have been treated in this way and yet the value of these treatments is not established beyond doubt. The problem is still being discussed in emotional rather than factual terms under such headings as "The Insulin Myth" (Bourne, 1953). The correspondence which followed that paper further demonstrated the widely differing views on the subject. This state of affairs does not surprise anyone who scrutinizes the literature which has accumulated over the years, and which contains results which are as diametrically opposed as the following examples illustrate. Gottlieb and Huston (1951) reported on 336 patients of whom 128 had psychotherapy, 65 insulin coma therapy, and 143 electro-convulsive treatment. There was little difference in the outcome of these three groups. On the other hand, Garmany (1946) claimed 56% remissions in cases treated with insulin coma compared with but 2% remissions in those not receiving such treatment. Cossa, Bougeant, and Lombard (1948) found curiously that in comparing insulin-coma treated cases in 1938 and 1944 there was a fall in remission rate from 43.7% to 28%. Kalinowsky and Hoch (1952) and Kalinowsky and Worthing (1943), recognized authorities on physical treatments in psychiatry, regarded insulin coma as inferior to electro-convulsive therapy in this disease. These authors are quoted as examples of the extreme differing and opposing views but theirs are not necessarily the most convincing papers on this topic.

Several workers, such as David (1954), Hughes (1953), Lewis (1945), and Malamud and Render (1939), have discussed the reasons for the confusing results reported, and have criticized the methods of investigation to assess the value of those treatments which have been used in the past. The problem was well summarized by Malamud and Render (1939). They enumerated some of the common errors in the reported studies on the outcome of schizophrenia ;

for example, too few cases, inadequate follow-up period, lack of uniformity in evaluating the symptomatology, varying criteria of diagnosis, inadequate examination of material, the variation in the intensity and kind of treatment, and the effect of the preconceived notions of the investigators on the material collected. Lewis (1945) has discussed the inherent difficulties in assessing the psychiatric case material in relation to the same problem.

With such formidable difficulties to be overcome nothing less than a designed experiment with suitable control group consisting of several hundred cases and followed over several years would be adequate. Such an undertaking would call for large resources and several years of observation, and so far no such study has been reported in the literature. Nevertheless there have been a number of valuable studies which, although not ideal, obviate some of the above-named errors. For instance, Silverman (1941), at the Meninger Clinic, and West, Bond, Shurley, and Meyers (1955) with his co-workers at the Philadelphia State Hospital have used material where the treated and control group both came from the same clinic. They have assessed results by comparing groups of patients who were admitted before and after the advent of the physical method of treatment. Such an approach will tend to minimize errors such as differing standards of diagnosis or extreme variation in the admitted case material. It also minimizes differences in the general management of patients, and marked variations in the application of therapy. Another problem is that of excluding the bias which arises from the selection of patients for treatment. The criteria which are recognized as guides for this selection are often also of a certain prognostic significance. A group consisting of treated patients only does not therefore warrant comparison with an untreated group which includes all types of cases indiscriminately. Bond (1954) again has tried to exclude this bias by comparing groups of schizophrenics, say all admissions of one year irrespective of whether they had treatment or not, with a similarly defined group observed

after the modern physical methods of treatment were known.

Owing to the foresight of Guttmann, Mayer-Gross, and Slater (1939) a similar opportunity offered itself to us. These authors reported a group of schizophrenic patients who were admitted to the Maudsley Hospital before the modern physical methods of treatment were used at that hospital. One of the stated reasons of their report was to have an "untreated" control group for future assessments of treatments. This has enabled us to compare an equivalent group of patients who were admitted to the same hospital after insulin coma and electro-convulsive therapy had been introduced.

We present a comparison of the outcome of the illness at the time of discharge from hospital of two groups of schizophrenic patients, of which one was not treated by either insulin coma or electro-convulsive therapy, whereas the other, while in all other ways comparable, includes patients who were so treated. Owing to the nature of this investigation the control group antedated the other by some 15 years. A follow-up study of the same case material is in preparation.

Material and Method

The 1934-35 Group.—This group, which will be called the "control group", was investigated by Guttmann and others (1939) and its characteristics were as follows:

(1) It consisted of all the schizophrenics discharged from the Maudsley Hospital between January 1, 1934, and December 31, 1935. (2) These patients had *prima facie* a favourable outlook owing to the admission policy of the hospital. (3) All patients were excluded who were over 46 years, the onset of whose illness antedated admission by more than 12 months, or in whose cases there was the slightest doubt as to the diagnosis.

(The case notes and protocols of these patients together with the most valuable comments by the investigators have been very generously made available to us for the purpose of this investigation.) The characteristics of the group together with the comparable data in the test group are set out in Table I.

From the control group we have rigorously excluded all patients in whom we were not satisfied that we were dealing with the first attack of the illness. This was done although careful comparison with the total group of patients originally described shows that the results were not materially altered.

The 1948-50 Group.—This group, which includes treated and untreated patients, will be referred to in this paper as the "test group". It includes all patients between the ages of 16 and 46 years who had no previous attacks, whose illness was of less than 12 months' duration, and who were admitted between January 1, 1948, and December 31, 1950, as in-patients to the Bethlem Royal Hospital and the Maudsley Hospital with a diagnosis of schizophrenia. They are in general comparable to the control group. From Table I it is apparent that the two groups differ only in composition with regard to diagnostic subgroups. This point and its implication will be discussed later.

As far as the treatment of this group is concerned, it falls into four classes. Those who were given (1) insulin coma therapy, (2) electro-convulsive therapy, (3) a combination of the two, and finally (4) those who had no such treatment. The precise composition of these groups is evident from Table III analysing the results.

The patients were admitted under the care of different clinicians on the staff of the hospital, who made the diagnosis and selected the patients for treatment. As far as the diagnosis is concerned this was scrutinized by the present authors before the

TABLE I
ANALYSIS OF COMPOSITION OF TEST AND CONTROL GROUPS COMPARED

	Control Group			Test Group		
	Male	Female	Total	Male	Female	Total
Patients No. %	55 40	86 60	137 —	73 47	83 53	156 —
Average age and standard deviation	25.6 ± 7	28.6 ± 7.8	27.4 ± 7.4	30.1 ± 7.7	27.2 ± 6.9	28.7 ± 7.2
Average duration of stay in hospital (in months) ..	4.4	4.1	4.2	4.5	5.4	5
Average duration of illness from onset of symptoms to admission to hospital (in months)	5.2	4.7	4.9	5.6	4.7	5.1
Percentage composition of diagnostic subgroups:						
Hebephrenic			29			24
Paranoid schizophrenic			38			32
Catatonic schizophrenic			29			10
Atypical schizophrenic			4			34

case was included in this group. Only a negligible number, however, had to be rejected because of doubts as to the accuracy of diagnosis.

The Treatments

Insulin Coma Therapy.—This treatment was based on the technique originated by Sakel (1935). All patients in the treatment group who had insulin coma were treated in the Insulin Department of the Bethlem Royal Hospital. This department applied the treatment generally in the way described by Sargent and Slater (1954). The procedure remained uniform throughout the years under investigation. At every treatment deep coma is aimed at and maintained for 20 minutes. The average number of comas in this group was 33.2 with an S.D. of 7.8.

Electro-convulsive Therapy.—This was given with a Strauss-Macphail apparatus after modification by an intravenous injection of "pentothal", 0.25 g. and C 10, 3 mg. The average number of treatments was 8 (S.D. 2.3). The method in general use in this hospital was described in detail by Davies and Lewis (1949).

Combined Therapy.—This method of treatment consisted in the application of E.C.T. during sopor: "interruption" followed at once by intravenous glucose.

Whether a patient was selected for treatment or not, and what type of treatment was given was decided by the clinician in charge of the case. Since the clinicians concerned were working quite independently of each other the methods of selection varied a great deal. Whether treatment is given depends of course on the general views held by the clinicians concerned. Some hold that where the prognosis is very poor the risks which the treatment involves are not justified by the small possibility of a remission, and their untreated group will therefore be mainly composed of patients with poor prognoses. Others will select those very cases for treatment as their chances of a spontaneous remission are small, and they should be given every chance of overcoming their illness. As the clinicians who were in charge of the present series include both schools of thought, our total group is naturally a very mixed one. The large variation in these views illustrates again the lack of accurate and precise knowledge on the efficiency of these methods of treatment. Other reasons for not giving treatment might be various, e.g., refusal of treatment by the patient, intercurrent illness, or such rapid improvement that treatment was not felt to be justified. The overall effect would seem to make a random selection of patients for various methods of treatment.

Since the test group involves both treated and untreated patients the results will not be biased whatever the composition of the treated section of the group may be.

Scrutiny of Records

The present investigation consisted only in the scrutiny of case records made by the clinicians in charge of the cases. This applies equally to the test group and the control group. The authorities previously referred to have pointed to the difficulties which beset this type of investigation. We shall deal with the more important points raised by them in turn as they apply to this study.

Age and Sex.—As shown in Table I the two groups are comparable in these respects.

Duration of Illness.—Both groups only include patients with first attacks, and whose illness has lasted less than one year. Table I, giving more detailed information on the duration of the illness, shows that the two groups are very similar in this respect.

Diagnosis.—The question of the diagnosis of schizophrenia is a recurrent problem, but the difficulty is not so much that of the diagnosis of schizophrenia *per se*, as of the classification of the patients into the diagnostic subgroups and varieties of schizophrenia. It is well known that one and the same patient may, in the course of his illness, present a varying admixture of symptoms and signs at different times which may cause him to be diagnosed as hebephrenic, catatonic, paranoid schizophrenic etc. In the case of the control group four subgroups were distinguished—hebephrenic, catatonic, paranoid schizophrenic and paraphrenic. In 1948 to 1950 a diagnostic code was in use at the Bethlem Royal and Maudsley hospitals based on the "Revised Diagnostic List" taken from the "International Lists of Diseases and Causes of Death, Geneva 1947". This coding was used in the preparation of the Tables.

In the test series the hebephrenic and schizophrenia simplex cases were considered together since it is recognized that the differential diagnosis in the early stages is not easy (Curran and Guttmann, 1945). The percentage of the total is comparable in the two groups. The paranoid schizophrenic group would seem to be strictly comparable in the two series. The atypical group in the test series includes paraphrenics, schizo-affective disorders, acute schizophrenic reactions, and otherwise atypical forms of schizophrenia. We are satisfied that the diagnosis of schizophrenia was a legitimate one in every case. The paraphrenic group of the control series falls readily into the atypical category.

There are, however, more atypical cases in the test series. The catatonic schizophrenics are fewer in the test than in the control group. This discrepancy is not easy to explain. It is possible that the atypical groups and the catatonic groups overlap to some extent. For example, the category "acute schizophrenic reaction" may fall into the atypical group or into the catatonic group, depending to some extent on the views of the individual clinician. It will be seen from Table I that the two series have comparable percentages if the catatonic and atypical cases are combined into one group, suggesting that this may be a correct explanation. The differences are emphasized here in view of the differences in the outcome. This will be discussed later.

Selection for Admission.—The two groups have been admitted to the same hospital with the admission policy unchanged. The Bethlem Royal and Maudsley Hospital being a teaching hospital does of course select its admissions to a certain extent. Only voluntary patients are being admitted, and patients with chronic illnesses and very bad prognoses are mostly excluded. As far as duration of illness is concerned we have only included patients with less than one year's history. We have set out to compare a largely treated group of schizophrenic patients with an untreated group; the selection methods of the hospital will not affect the results provided they have not changed. Because of this selection the findings in these groups may not, of course, be applicable to schizophrenic patients in general, but since the physical methods of treatment are usually thought to be most effective in "fresh" cases, the results in the two groups which consist of that type of case should be of particular interest.

Selection for Treatment.—We have already pointed out that the indications used for selection for treatment as such and for the different types of treatment varied widely. The treated and untreated sections within the test group are not at all comparable. Nor are the treated patients alone comparable with the control group. We do not know the exact criteria of selection which applied to each patient. It is therefore possible that the treated section would tend to be biased by containing more of a certain type of patient than the untreated section. In order to avoid this source of error which beset many previous investigations, we have not compared the outcome of the treated patients alone but have taken *all* schizophrenic patients who have passed through the hospital within the stated period. If treatment by the physical methods has any benefit the test group should on the whole show a better outcome than the control group.

The classification of outcomes in the test group was standardized in the following categories: (1) Recovered, (2) much improved, (3) improved, (4) slightly improved, (5) unchanged, (6) worse, (7) dead, (8) suicide. The assessment was that of the clinician in charge of the case. In the control group the assessment of the result on discharge was stated in comparable categories, and there was no difficulty in translating these into the code used above, which had been adopted in the hospital at a later date.

Results and Discussion

Effectiveness of Physical Treatment.—As a first step we shall attempt to evaluate the effect of physical treatment on schizophrenia without any reference to the particular type of treatment. As is well known the assessment of the degree of improvement is very difficult and always subjective to a certain extent. In order to simplify the assessment we are in the first instance only comparing "improved" with "not improved", ignoring for the moment the degree of improvement. "Improved" includes the categories recovered, much improved, improved, and slightly improved; "not improved" includes the categories unchanged, worse, and dead. Table II shows the outcome on discharge from hospital in the test and control groups for comparison.

If the test and control groups are compared as a whole, ignoring for the moment the question of treatment within the test group, the relevant figures are for the control group: improved, 50 cases (35%), not improved, 87 cases (65%); for the test group: improved, 107 cases (68%), not improved, 49 cases (32%). This difference is highly significant statistically ($P < 0.01$). The outcome in the test group is much better than in the control group. Since the two groups are in other respects comparable this would strongly suggest that the difference is due to physical treatment. If that were so the same trend should be apparent within the test group itself if the treated and untreated sections were compared. Table II shows the results when

TABLE II
COMPARISON OF CONTROL GROUP WITH TREATED AND UNTREATED SECTIONS OF THE TEST GROUP

	Test Group		Control Group
	Treated Section	Untreated Section	
	Number of Patients	Number of Patients	Number of Patients
Improved ..	80 (78%)	27 (51%)	50 (35%)
Not improved ..	23 (22%)	26 (49%)	87 (65%)
Total ..	103	53	137

the test group is broken down in this way. Comparing these two sections there is a considerable and significant difference between the treated and untreated. The results in the untreated section, however, are better than in the control group and this difference is significant at the 5% level. This in itself casts some doubt on the absolute validity of the first conclusion. Were treatment alone responsible for the difference between the two series, it would be expected that the untreated section would show results similar to or worse than the controls. This is not the case, and the untreated section, while not so good as the treated section, has still done better than the control group. The suggestion is that factors other than treatment must also play a part in the apparent improvement; for example, the case material may have been in some respects dissimilar. To investigate this point the same comparisons were made with the material broken down into the various diagnostic subgroups.

Hebephrenic Group.—At once it is evident (Tables III and IV) that as far as the hebephrenics are concerned the figures in the test group and control group are similar. The control group has 43% improved compared with 45% improved for the test group. There is, however, a distinct difference when the treated and untreated sections of the test group on the one hand, and the control group on the other hand, are compared. The un-

treated hebephrenics did very much worse than the control group, and the treated hebephrenics better by 19%. This suggests that in fact a better prognostic group was selected for treatment and a worse left untreated. The conclusion from this is that physical treatments did not materially affect the outcome in this group of hebephrenics.

Paranoid Schizophrenic Subgroup.—In the case of the paranoid schizophrenic group, the outcome of the test group as a whole is superior to the control group (Tables III and IV). Forty-seven per cent. of the control group improved compared with 63% of the test group. The outcome of the untreated section of the test group of paranoid schizophrenics is similar to that of the control group, while that of the treated section is superior to both. In this case it seems reasonable to suppose that the improvement is due to the physical treatment, although the evidence is not conclusive.

Catatonic and Atypical Subgroups.—Lastly there are the catatonic and atypical groups which can be dealt with together as the diagnoses probably overlap and as the figures in the two groups show similar trends (Tables III and IV). We find that the test group as a whole with 79% improved did very much better than the control group with 69% improved. In fact the difference is more striking than in either of the other diagnostic subgroups. If, however, the treated and untreated sections of

TABLE III

COMPARISON OF DEGREE OF IMPROVEMENT IN DIAGNOSTIC SUBGROUPS OF CONTROL AND TEST GROUPS, AND IN TREATED AND UNTREATED SECTIONS OF THE LATTER

	Hebephrenic Schizophrenia			Paranoid Schizophrenia			Combined Catatonic and Atypical Schizophrenia		
	Control Cases 40	Test		Control Cases 52	Test		Control Cases 45	Test	
		Treated Cases 26	Untreated Cases 11		Treated Cases 30	Untreated Cases 19		Treated Cases 46	Untreated Cases 23
Improved (%)	43	62	9	37	80	37	31	80	78
Not improved (%)	57	38	91	63	20	63	69	20	22

TABLE IV

COMPARISON OF OUTCOME OF TEST AND CONTROL GROUPS IN DETAIL

	Hebephrenic		Paranoid Schizophrenic		Catatonic and Atypical Schizophrenic	
	Control Cases 40 (%)	Test Cases 37 (%)	Control Cases 52 (%)	Test Cases 49 (%)	Control Cases 45 (%)	Test Cases 69 (%)
1. Recovered	8	13	10	6	2	33
2. Much improved	2	11	4	31	2	22
3. Improved	23	5	19	12	27	14
4. Slightly improved ..	10	16	4	14	—	10
5. No change	57	51	59	37	67	18
6. Worse	—	3	2	—	2	3
7. Died	—	—	2	—	—	—

the test group are compared (Table III) the expected difference is not found. Instead it will be seen that the outcome in the untreated section is very much the same as that in the treated section. Again we are driven to the conclusion that factors other than treatment must be involved to account for the differences in the two groups.

The final conclusion is therefore that it is only the paranoid schizophrenic group that seems to show a large response to physical treatment. There is no evidence, in differences of duration of illness, mean age, or sex distribution, that the paranoid schizophrenic group were more favoured in the test than in the control series, and if factors other than physical treatment were operative, they are not immediately apparent.

Effectiveness of Different Types of Physical Treatment.—It will be seen from Table V that by

TABLE V

NUMBER OF PATIENTS RECEIVING ONE OR OTHER OF VARIOUS TYPES OF PHYSICAL TREATMENTS WITH THE RESULTS IN THE TEST GROUP

	Insulin Coma Therapy	Combined Insulin Coma and Electro- convulsive Therapy	Electro- convulsive Therapy	No Treat- ment
	Number of Patients	Number of Patients	Number of Patients	Number of Patients
Improved ..	48 (81%)	20 (74%)	12 (71%)	27 (51%)
Not improved ..	11 (19%)	7 (26%)	5 (29%)	26 (49%)
Total ..	59 (38%)	27 (17%)	17 (11%)	53 (34%)

far the larger proportion of patients had insulin therapy alone or combined with E.C.T. A minority had E.C.T. alone. As far as these small figures permit any conclusion it would seem that there is little to choose between the various methods. Since, however, the paranoid schizophrenic group shows the most convincing response to treatment we have analysed this group further as regards types of treatment. The insulin-treated section is numerically by far the largest (23 of 32 treated) so that the other forms of treatment are not likely to have affected the results appreciably. Of the 23 insulin-treated cases, 22 showed improvement. The effectiveness of treatment in this group would therefore appear to be due to insulin coma therapy and not E.C.T. or the combined insulin and E.C.T. The comparative value of these methods, however, cannot be assessed from our figures with any degree of confidence.

Assessment of the Results.—The better results apparent in the paranoid schizophrenic group may

not be due to the physiological effects of insulin. It has been pointed out before that the care, attention, and optimistic therapeutic environment of a busy insulin unit may in themselves be conducive to the improvement. It has even been asserted that this is the only cause for any apparent improvement. The fact that the other diagnostic subgroups did not generally respond in the same favourable way, although exposed to the same régime, tends to cast doubt on such a notion. It can, however, be argued that the different psychopathology of the paranoid schizophrenic may make him specially susceptible to the particular measures employed in an insulin unit. The present investigation cannot answer this question. A different type of experiment would be necessary to test such a hypothesis.

In the presentation of results so far, no attention has been paid to possible qualitative differences in the groups as regards outcome. The varying degrees of improvement have been represented as a comprehensive single figure. Table IV shows how the groups compare with regard to the more detailed description of the outcome. It will be seen that the trends described hitherto are essentially unchanged. A more detailed breakdown of the figures of Table IV, which is not presented here in full, suggests that there is some advantage to the test group hebephrenics as regards total recovery, which could be attributed to treatment. Similarly, in the catatonic and atypical subgroup of the test group, the treated section has an 11% advantage over the untreated as regards "total recovery" (37% to 26%) and a 7% advantage as regards "much improved" (24% to 17%). However, in the other categories of "improved" and "slightly improved", the untreated section is superior.

It is difficult to draw precise conclusions from these figures, and the question must be left open.

There remains the puzzling finding that the catatonic and atypical group seem to have a much better short-term prognosis in the test group than in the control group, and that independently of whether they had treatment or not. A possible explanation could be that the nature of the illness has changed in the course of the years (Bourne, 1953). We must state that perusal of the case histories of the control and test groups did not impress us by any marked difference in symptomatology. Furthermore in whatever way the test group may differ from the control group, the difference is maintained consistently in each of the three years 1948, 1949, and 1950. Harris and Norris (1954) showed in a very interesting study that mental hospital populations have changed in the course of time. This change is closely linked

with the major alteration in legislation referring to mental illness due to the introduction of the Mental Treatment Act 1930, and they concluded that this Act brought a different type of patient into the mental hospital, with better prognosis. As far as the Maudsley Hospital is concerned this factor can only be thought of as applying in a very limited way, since, as a teaching hospital, it has always admitted voluntary patients, the majority of whom had a good prognosis. Another factor which may be of great importance is the therapeutic optimism in psychiatric hospitals with its effect on the doctors and other staff and secondarily on the patients. These theories could be tested by comparing similar figures from other hospitals for suitably selected periods. As yet they can only be accepted as purely speculative though not unlikely.

Summary

The outcome of the illness at the time of discharge from hospital of two groups of schizophrenic patients is compared. One group was observed before, the other after, the introduction of the modern physical methods of treatment, namely electro-convulsive therapy (E.C.T.) and insulin coma therapy. The two groups are comparable in most relevant respects. They are designated the control group and the test group respectively.

The test group does better as a whole than the control group, but further analysis suggests that factors other than the physical methods of treatment may be concerned.

Treatment by insulin coma and E.C.T. seems to benefit the group of paranoid schizophrenics most convincingly, although even that is not conclusive.

An additional finding is that the short-term prognosis of catatonic and atypical schizophrenia appears to have undergone a change for the better. This cannot be attributed with certainty to the insulin coma or electro-convulsive therapy.

Possible explanations for this change in prognosis are discussed.

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