A CONTROLLED TRIAL OF HYPOTHERMIA IN CHRONIC SCHIZOPHRENIA

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Introduction

Physical methods play an important part in psychiatric treatment. The roles of electroconvulsive therapy and, to a lesser extent, insulin coma therapy, are fairly well-defined and their effectiveness recognized, though different authorities qualify their recognition in various ways.

In searching for a new physical method it is reasonable to look first for a common factor in the therapies which have achieved some success. Insulin coma and its dangerous but effective complication "irreversible" coma, are both associated with the cessation or reduction of higher neuronal activity, or disruption of its organization. Electroconvulsive therapy depends for its effectiveness on the production of an epileptic fit and this results in temporary cessation of cortical signalling activity if electro-encephalographic silence can be so interpreted; Gastaut (1) suggests that the major fit is the outward sign of a rhythmic inhibitory system which produces cortical extinction. If cessation of existing neuronal activity were a common factor it would be sensible to look for other ways in which this could be brought about.

The number of possibilities is limited. Methods such as hypoglycaemia, hypoxia and sedative drugs, though effective in certain types of case, reduce not only the capacity of the neurone to discharge but its ability to maintain its own integrity. It follows that the risk of neuronal death is high if the therapy is vigorously done. It might be possible, by artificially induced specific hypovitaminosis, so to disrupt enzyme systems within the neurone that the cell failed to function but remained viable; neuronal sparing in spite of severe hypofunction in Wernicke's syndrome has been described. To use hypovitaminosis therapeutically would be a very cumbersome procedure.

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On the other hand temperature reduction, if carried far enough, would be likely to reduce neuronal activity and at the same time the maintenance metabolic needs of the cell. It would therefore be reversible and unlikely to cause neuronal damage. To suggest hypothermia as a physical treatment is only to echo other workers (2, 3), but in view of the successful introduction of hypothermia into surgery it now seemed reasonable to attempt its psychiatric application. Accordingly it was decided to conduct a controlled trial of this treatment on a small number of patients which, if the results were encouraging, would be expanded later. This paper reports the conduct and results of the pilot scheme.

METHOD

(a) *Selection of Patients*

It was not possible to predict what mental changes, if any, would occur as the result of hypothermia. It was felt that the patients treated should have a wide range of symptomatology and should have failed to respond to previous treatment. Further, their prognosis should be bad and if possible they should be in a steady state as far as the level of their symptoms was concerned. Chronic schizophrenics were thought to be suitable. To reduce risk only physically fit patients under forty-five years of age, free from obesity, chest disease or electrocardiographic abnormality, were selected. Fourteen pairs of patients were matched for age, duration of illness, ward, and, where possible, diagnostic subgroup. The patients were all male and came from Horton or Springfield Hospitals.

Patients came in pairs to Atkinson Morley's Hospital and were assessed, before and after treatment, by interview and psychological testing. One of each pair had an anaesthetic with hypothermia, while the other had an anaesthetic producing the same period of coma but at normal temperature, as described later. The recipient of hypothermia was decided by a randomizing method supplied by Dr. Fairbairn. Successful precautions were taken to arrange that those who assessed the patients did not know which was the experimental subject and which the control.

(b) *Selection of Temperatures*

Reports of cases of accidental hypothermia show that consciousness is lost at 28–30° C. It was decided to cool all the experimental group down to 30° C. and keep them at this temperature for one hour. Surface cooling by means of ice bags was the method adopted.

(c) *Treatment*

Pre-medication. To facilitate accurate assessment it was essential to maintain the patients on any sedative or tranquillizing drugs that they were accustomed to receive. The drug most commonly employed was chlorpromazine. On the day of treatment all drugs were stopped and immediate pre-medication obtained by omnopon gr. 1/3 (20 mg.) and scopolamine gr. 1/150 (0·4 mg.) in the early cases, but later this was changed to pethedine 100 mg. and atropine gr. 1/100 (0·65 mg.).

Anaesthetic Technique. Anaesthesia was induced with a small dose of thiopentone and oral intubation carried out under suxamethonium. Owing to the difficulty of performing venepuncture at low temperatures, an intravenous transfusion of dextrose-saline was set up and all subsequent injections

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given into this drip. Maintenance of anaesthesia was achieved by a mixture of oxygen and nitrous oxide in equal proportions, to which ether was added as required. Further muscle relaxation was obtained by the use of d-tubocurarine. Respiration was manually controlled through the treatment, a carbon dioxide absorbing apparatus being included in the anaesthetic circuit.

Hypothermia. Once anaesthesia was established an E.C.G. monitor was set up and an electrode of a thermo-couple placed in the oesophagus to record temperatures. The naso-pharyngeal temperature was registered on an alcohol thermometer lying in the nose. Recordings of pulse rate, blood pressure and temperatures having been noted, the patient was cooled by the application of three plastic pillow cases partially filled with crushed ice. These were placed so that they encircled the patient's trunk. Pulse rate, blood pressure and temperature were recorded at five-minute intervals until a temperature of 31½°C. was reached. The ice was then removed and an after-drop of 1½° C. was usually obtained. It was observed that by this method patients weighing between 9 and 12 stones lost one degree Centigrade every fifteen to twenty minutes.

Re-warming. Patients were re-warmed by means of plastic water blankets, water being pumped through them at 45° C. Warming was continued until a temperature of 35° C. was attained. At this stage patients were allowed to wake up; the young shivered but the elderly and those accustomed to receiving generous doses of chlorpromazine did not do so.

Control Patient. The control series of patients were treated in a like manner to the above except that ice was not applied. The period of anaesthesia was similar to that undergone by the cooled patients.

(d) *Psychological Testing*

The selection of tests had to take into account not only the self-evident criterion of an objective and valid measure of psychoticism (that is, in this context, of chronic schizophrenia) but also tests which would be easily administrable to a group of chronic schizophrenics. These are described in detail below:

(i) *Figure Reconstruction Test.* This test requires the reproduction of geometrical designs from memory, as developed by Brengelmann at the University of London Institute of Psychiatry. The present form represents a level of difficulty well below a mean level and involves a number of different measures, all objectively scored, of error and expressive movement (4).

The reproduced designs are scored for:

(*a*) Rotation error of the individual shapes around a central reference point. The scores are expressed in degrees. This involves, of course, memory of the placement of the figures.

(*b*) Distance in millimetres from the centre of the individual shape to a central reference point.

(*c*) Size which is expressed in 1/10 millimetre. These latter two scores are of expressive movement.

A further addition to the memory portion of the Figure Reconstruction Test is the recognition section. Thirty patterns, ten of which are actually presented in the memory test are assembled on a recognition card. Subjects are asked to give two statements; firstly whether they think they have seen a particular pattern before during the memory test, and secondly how certain they feel about the correctness of their statement. From this three scores are derived:

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1. Positive recognition or the number of "Yes" answers, i.e. number of times the subject thinks he has seen the pattern before irrespective of the correctness of the statement. This score is interpreted as over-inclusion.

2. Certainty in response to the task. The subject is made to choose one of four degrees of certainty (+2, +1, −1, −2). Scores are expressed as means per judgment carried to two decimals.

3. Adequacy of certainty. This score is computed by deducting mean certainty for incorrect responses from mean certainty of correct responses. The subject is said to respond adequately when more certain responses are attributed to the correct answers than to the incorrect ones. Limitations of the not yet fully developed scores of this latter have been expressed by the author (4).

(ii) *Picture Recognition Test.* This test consists of two sets of six pictures. Each was presented in a special box as described (7). The pictures represent commonly known objects, e.g. a pair of spectacles, hands, a human figure, etc. (6). Each picture is shown with the following time exposures: two at 1/100 second, two at 1/5 second, two at ½ second, two at 1 second, two at 3 seconds, one at 30 seconds. The score is the number of exposures required for recognition over the entire set of six cards.

(iii) *Epstein Over-Inclusion Test.* This is a paper and pencil test consisting of a list of fifty words. Each of these is followed by six response words from which the subject is asked to select however many he regards as a necessary part of the concept described by the stimulus word. The test was developed by Epstein (8) and additional information has been derived from the work of Payne at the Institute of Psychiatry (9, 10).

Predictions

1. The results of previous experiments give the following norms for a group of acute psychotics on the Figure Reconstruction Test (5):

	Mean
Rotation error	35·1
Size	126·8
Distance	48·3
Positive recognition	63·5
Certainty	152·7
Adequacy	16·9

The mean scores on the above for the present group should all be the same or higher with the exception of adequacy which should be lower, on the pre-treatment trial.

2. The mean score of the Picture Recognition test on an acute psychotic group was 55·8 (6).

The mean scores of the present study should be the same or higher on the pre-treatment trial.

3. The mean score of a group of schizophrenics on the Epstein Test established in a previous study was 51 (10).

The mean score on pre-treatment in this series should be the same or higher.

4. There should be a significant difference between the experimental and control group scores following treatment.

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Method

The patients were tested immediately on admission to this hospital and the day after treatment either by the psychologist or by the nursing staff under the psychologist's supervision.

There were three forms of equivalent difficulty of the Figure Reconstruction test (one for practice) which were randomly varied in presentation. Ten cards were presented in each form using a 30-second exposure time.

Two forms of six cards each of the Picture Recognition test were presented also randomly varied.

The Epstein Over-Inclusion test does not have an equivalent form so the same test was given after treatment.

Co-operation of the patients was secured in all but two cases, one being a mental defective prior to the onset of the illness and the other, a paranoid patient, refused the test.

The results were analysed by t tests for correlated means in small samples. Twelve pairs of scores were used for the Figure Reconstruction test, eleven pairs for the Picture Recognition test and six pairs for the Epstein Over-Inclusion test.

The means and variance were calculated for the combined groups on the pre-treatment trials giving an N of 24 for the Picture Reconstruction test, an N of 22 for Picture Recognition test and an N of 19 for the Epstein Over-Inclusion test.

Interview Assessment

All patients were interviewed on the day before and the day after treatment, each separately by two observers (P.H. and G.W.), who, after an interval of about a month, did further interviews at the hospital of origin. Interviews were designed to suit the requirements of the Wittenborn Scale for rating currently discernible psychopathology, the sections of the scale used being those applicable to schizophrenic patients, viz. 5, 6, 7, and 8. Such items as could not be scored at interview were assessed at the source hospitals before and after treatment (11).

Results

(a) *Psychological Testing*

1. The mean pre-treatment scores on the Figure Reconstruction test confirm the prediction made with the exception of Certainty, which is lower than the previously established norms (see Table I). Inspection of the scores on this section of the test reveal that two patients out of twenty-four produced strong negative results. The rest were all highly positive and without these two yield a mean of 154.

Table I

Tests	Mean	Variance
Figure reconstruction:		
(*a*) Rotation error	60·13	534·4
(*b*) Size	135·17	2,842·4
(*c*) Distance	51·33	97·9
(*d*) Positive recognition	64·83	1,324·5
(*e*) Certainty	137·54	4,789·8
(*f*) Adequacy	5·71	1,057·3
Picture recognition	57·64	182·3
Epstein over-inclusion	47·00	681·6

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These results support Brengelmann's findings with the test and show it to be a valid and reliable measure of psychoticism producing predictable results.

2. The second prediction is supported by the results. The mean pre-treatment score is higher than previously established norms (see Table I) and confirm previous findings that this test is a reliable and valid measure of psychoticism.

No difficulty was experienced in administering these tests to a group of chronic psychotics except as above mentioned.

3. The Epstein Over-Inclusion test produces results which do not confirm the third prediction (see Table I). The mean score is lower than that established in previous studies. However, the result is in the direction of previous findings, does not differ significantly from previous results with schizophrenics and is significantly different from the mean score for neurotics of 17 (10).

Some difficulty was experienced in getting the patients to understand the procedure, hence the small number of results achieved for comparison (six pairs) and at the time of administration some doubt was felt as to the reliability of this measure with such severely ill patients. Reliability was therefore calculated for these results. The reliability of 0·79 indicates that despite the subjective impression, this test is a perfectly reliable measure even with chronic groups of schizophrenics.

4. No significant differences between control and experimental groups following treatment were obtained and therefore the fourth prediction is not confirmed.

Three different tests covering a wide range of measurements of psychoticism were used in the present study. All the results are in the direction predicted and reveal the tests to be stable and valid measures of the processes tested. Clear-cut results are obtained with the Figure Reconstruction test and it is particularly noteworthy that the measure of Over-Inclusion on this test (Positive Recognition) is not inconsistent with the Epstein, confirming previous observations that psychotics tend to have disturbances of thinking of this over-inclusive type.

With so wide a range of apparently satisfactory measures, the failure to find any significant differences between the control and experimental groups following treatment, suggests that hypothermia does not effect any alteration in chronic schizophrenics.

(b) *Interview Assessments*

Statistical analysis of the results failed to demonstrate any significant difference between the measured psychopathology of the control and experimental groups.

As is commonly the case, both experimental and control groups improved significantly for their change of surroundings and increase in attention.

(c) *Clinical Impressions*

Interviewers were struck by the correctness of their guesses about which patient had received hypothermia, the basis of their guesses being their impression that the patients who had received hypothermia were more outgoing and warmer in their emotional responses. The anaesthetist independently considered that some alteration took place in the cooled patients, saying that they

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were more "aggressive" on waking, "thrashing about" in a way quite distinct from the controls' mode of waking; and that for a few hours they were "more positive", "able to express themselves better", while "their answers changed from monosyllables to sentences".

This kind of change was not measured by the ratings we used. However, a different type of reaction following different treatments might be expected without implying an alteration in basic psychopathology.

Discussion

The experiment ruled out hypothermia, administered on a single occasion, as an immediately applicable form of treatment in chronic schizophrenia. The difficulties experienced in assessing the patients and the alterations in both control and experimental groups while they were being treated and observed do not call for special mention here.

A firm clinical impression of increased warmth and rapport distinct from any alteration in schizophrenic psychopathology, such as hallucinatory phenomena or delusion formation, was obtained. This was, however, fleeting, and the judgment may be contaminated by our having been able to guess correctly which patients had had hypothermia; one patient, not included in the series, received hypothermia three times and displayed the changes mentioned above to a remarkable degree, though the alteration was an improvement. At the time the experiment was planned no clue as to the likely alterations could be obtained, and an illness with a broad spectrum of symptoms was chosen to which a wide range of observations and measures were applied. Further work should include specific assessment of rapport and measures of the amount of spontaneous and induced interest manifested by the patient.

Further trials would be safer if they used either a temperature of, say, 34° C. maintained for a longer period, or if some method of local cooling of the brain or a part of it could be devised. More obvious and perhaps more prolonged changes might occur if patients less set in their psychoses were treated, or if cooling were done several times: repetition is necessary with other physical treatments.

In the first two cases undergoing hypothermia changes occurred in cardiac rhythm attributable to excess vagal tone. Both were cured by the use of atropine given intravenously. It was therefore decided to change the premedication to include this drug, and to couple it with pethidine. A further undesirable effect was observed in those patients accustomed to receiving large doses of chlorpromazine over a long period. At temperatures between 32° C. and 30° C. periods of circulatory failure occurred and in one case (not included in the series) it became necessary to warm the patient up without completing the treatment. Therefore it is recommended that in any future series the patients should be taken off chlorpromazine some time before undergoing hypothermia. Clearly, it would be unwise to attempt any experiment of this kind without the constant presence of the appropriate specialists and their equipment.

Summary

As part of an attempt to assess the effects of hypothermia on psychiatric patients, a group of chronic schizophrenics, divided into control and experimental groups, were appropriately treated and assessed by clinical interview and psychological testing. No significant differences, in the symptoms and signs measured, emerged. Clinical impressions of alterations are described and their implications mentioned.

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