THE EFFECTS OF NICOTINIC ACID, NICOTINAMIDE, AND PLACEBO ON THE CHRONIC SCHIZOPHRENIC

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FOR various reasons we became interested in the possibility that nicotinic acid or nicotinamide might be of some benefit to the chronic schizophrenic. Many workers have noticed clinical similarities between the acute schizophrenias and the encephalopathies of nicotinic acid deficiency (4). Nicotinic acid is known to be of value in pellagra (2) and in the treatment of delirium tremens and allied states (1), and Osmond and Hoffer have had promising results with these substances in the treatment of schizophrenia in its acute phase (3). There seemed therefore to be sufficient reason for an investigation of their effects in the schizophrenic in the chronic phase, for, as far as we are aware, the therapeutic possibilities have not been explored. Since patients often respond strikingly to the giving of any tablet, regardless of its contents, we also gave similar tablets of an innocuous substance, here referred to as Placebo. For convenience the three preparations employed will be referred to in future as *A* (Nicotinic Acid), *M* (Nicotinamide) or *P* (Placebo).

THE TEST

The group tested consisted of chronic schizophrenics, of ages from forty to seventy.

The design of the test was arranged so that certain errors were avoided. One of these was that different patients would tend to be at different clinical levels throughout the test. This fact can be allowed for by giving all three treatments to each patient, and then making comparisons only between results from the same patient, by taking differences say, so that each patient acts as his own control.

Another error is introduced by secular changes, whether by the patient being at first stimulated by the mere fact of being given something, or by the clinician's standard of what is "good" changing slowly throughout the test. These errors were avoided by testing the patients in triples, in which one patient

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received the drugs in the order *A*, *M*, *P*, while the other two received them in the orders *M*, *P*, *A*, and *P*, *A*, *M*. Thus each substance occurred once in the first place, once in the second, and once in the third. The *sums* over such a triple have the errors balanced out.

Such a set of three patients, chosen to be as alike as possible in age, clinical condition, sex, past history, etc., formed the primary block for the test. From this block the basic information that we require is obtainable. Random sampling was then reduced as far as was possible by the provision of further blocks, each as homogeneous as possible internally. Thirteen such blocks went through the test to completion, involving thirty-nine patients. Thirty patients (ten blocks) were of women, nine (three blocks) of men.

Some time might be necessary for the treatment to show its effect, but we considered that eight weeks on each substance might well be sufficient for any action to declare itself. Accordingly each substance was given for eight weeks continuously. One week without treatment was allowed between each eight week period; so the patient was under observation over twenty-six weeks in all.

In each eight-week period on one substance, the first week was used to raise the dosage to its maximal level. Three hundred mg. t.d.s. was given on the first day and each day the dosage was increased by this amount so that on the seventh day the dosage was 2·1 grams t.d.s. (i.e. 6·3 grams per day). This last level was then sustained for seven weeks.

Assessment

We were interested chiefly in the patients' *general clinical condition*, rather than in their response to specialized psychological tests (and in any case the chronic schizophrenic would often be quite unco-operative in the employment of any special tests). So we assessed the patients' clinical state by the following twenty-three criteria:

1. Does he have to be fed?
2. Has he been mute?
3. Has he talked to himself?
4. Does he sleep badly?
5. Does he daydream?
6. Does he keep to himself?
7. Does he laugh without cause?
8. Is he apathetic?
9. Is his behaviour childish?
10. Is he upset easily?
11. Is he untidy in his dress?
12. Does he hoard rubbish?
13. Has he been dirty in his habits?
14. Is he deluded?
15. Has he masturbated?
16. Is he destructive?
17. Is he suspicious?
18. Is he hallucinated?
19. Is he homicidal?
20. Is he suicidal?
21. Has he been impulsive?
22. Does he employ himself in any way?
23. Has he any interests?

Each question was answered by "Yes", "No" or "Variable". At the end of each fortnight the patient was assessed by the twenty-three questions, and a score derived. One point was given for each "Variable", two points for each "No" occurring in the first twenty-one questions and two points for each "Yes" occurring in the last two questions. Thus the maximal score at one assessment was 46; a high score corresponded to a good clinical condition.

The questionnaire was filled in by the Ward Sister who had had the patient under observation during the previous fortnight, in consultation with the psychiatrist. Each patient, over the twenty-six weeks, was thus given twelve assessments of his condition.

To ensure that the person filling in the questionnaire was unbiased, the three drugs were given in an order known only to the dispenser, who allotted one of the three orders mentioned above to each of the three patients. Thus

the person marking the questionnaire would know, on a particular week, that one of the patients was on nicotinic acid, one on nicotinamide, and one on placebo, but she would have no way of telling which was which other than by whatever was clinically observable.

In all, thirty-nine patients contributed to the test by completing the course. Although the whole group was, naturally, somewhat heterogeneous, the blocks of three were so arranged that each block was fairly homogeneous internally. As will be shown below, all the comparisons were made primarily within the blocks; thus the comparisons are based on material much more homogeneous than the total range of patients in the group.

RESULTS

It is convenient first to dispose of some minor matters. The thirty-nine patients mentioned above were those remaining after nine patients had refused to continue the treatment. One patient refused while receiving the acid, six during the amide, and two during the placebo. Although the refusals were mostly against the amide, the multinomial distribution shows that, as the probability of exactly one, two, and six is 56/729, i.e. about 1/13, the difference can hardly count as significant.

Nicotinic acid is, of course, well known to cause vaso-dilation. Each form recorded whether flushing had occurred, and the occurrences were divided into "slight" and "marked". The three substances gave flushings as shown in Table I

TABLE I

	Degree of Flushing			
	0	Slight	Marked	Total
Acid	106	42	12	160
Amide	146	13	1	160
Placebo	137	18	5	160
Total	389	73	18	480

Table I includes the results for one patient who completed the course but whose Block was not completed.

χ^2 is 36·7: n=4: p is less than 0·001.

It is clear that the nicotinic acid produced flushing much more than the others. One cannot help noticing, however, that the nursing staff, otherwise highly trustworthy, have recorded flushing in no less than twenty-three occasions when the patient in fact was on placebo. We do not regard this as a suggestion that the staff was unduly careless; we regard it rather as showing how essential it is that any question involving some degree of judgment should be made in ignorance of the factor at work.

We can now turn to the main matter of interest: whether, if the drug acts quickly, the general level of clinical condition tends to be better on either of the two drugs than on the placebo.

For this purpose the four scores (over the 8 weeks under each drug) were added together. Thus, each patient now gave three totals, one for acid, one for amide and one for placebo occurring in some order. The three patients in a block each gave three results, forming a Latin square. Thus, patients Nos. 13, 14 and 15 gave the scores shown in Table II, where the columns show the three periods, and the letter after each entry shows the drug given.

TABLE II

Patient No.	Period 1	2	3
13	127 (*A*)	121 (*M*)	118 (*P*)
14	95 (*M*)	108 (*P*)	109 (*A*)
15	134 (*P*)	176 (*A*)	174 (*M*)

The difference between rows represents the fact that, e.g., patient 15 was consistently in a better clinical condition than patient 14. The difference between columns reflects the fact that secular changes (such as a drift in the markers' standards) might be occurring. The other differences show the usual effects of treatment or of interaction. Thirteen blocks provide the necessary replication.

The analysis of variance of the 117 observations need not be given in detail. The essential part occurs in Table III, which gives the totals for the treatments.

TABLE III

Period 1	2	3
1,504 (*A*)	1,641 (*M*)	1,590 (*P*)
1,525 (*M*)	1,687 (*P*)	1,654 (*A*)
1,610 (*P*)	1,705 (*A*)	1,736 (*M*)

A=4,863 M=4,902 P=4,887 F_1=4,927 F_2=4,005 F_3=4,820

It also gives (as F's) the three diagonal totals whose differences represent high-order interactions. What interests us especially are the differences between the totals for *A*, *M*, and *P*.

The eight degrees of freedom in Table III can be divided into the following:

1. Two degrees of freedom between columns; these are of no interest since they represent secular changes in the experiment, and are required only for elimination.

2. Two degrees of freedom between rows; these represent differences between three sets of 13 patients, and are required only for elimination.

3. Two degrees of freedom between the treatments *A*, *M*, and *P*. These may meaningfully be divided into one degree of freedom which compares the condition under placebo with the average condition under acid and amide, and one degree of freedom which compares the acid and the amide.

4. Two degrees of freedom due to high-order interaction; they are represented by the variance between the three totals *F*, and provide the appropriate estimate of error.

The analysis is shown in Table IV

TABLE IV

Variance	D.F.	Sum of Square	Mean Square
Acid *v.* Amide	1	19·5	19·5
Placebo *v.* Drug	1	0·3	0·3
Rows	2	1292·7	—
Columns	2	2344·7	—
Interaction	2	163·8	81·9
Total	8	3820·9	—

In the Table the divisors used in forming the sums of squares have been those appropriate to the full analysis of 116 degrees of freedom.

The results in the right-hand column show unequivocally that there is no evidence for any change in the clinical condition so far as a general change in the level is concerned. "Drug" is not significantly better than placebo, and the two forms of the drug show no significant difference.

There remains the possibility that the drugs may have had a cumulative effect, so that the clinical condition at the end of the eight weeks' treatment was significantly different from that at the beginning. This question can be examined simply by using, as the estimator over the eight weeks, not the sum of the four scores but the difference between the last and the first. The difference under nicotinic acid can then be compared with that under the amide, and so on. The null hypothesis is then that these quantities are normally distributed about zero, so *t*-tests are appropriate. Again the two main matters of interest were:

1. Whether the change under placebo differed significantly from the average change under the drugs (within each triple);

2. Whether the acid and the amide differed in the amounts of change they produced.

T-tests showed, in fact, that both the changes were insignificant.

Summary

The effects of massive doses of nicotinic acid and of nicotinamide were tested on the chronic schizophrenic, together with an inert placebo. Thirty-nine patients were tested, each over 24 weeks. The results were assessed on a prepared scale.

Analysis of the results failed to show any evidence that the treatments were influencing the patients.

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