INFERENCE AND SUGGESTION IN A CLINICAL TRIAL
(NIAMID IN MONGOLISM)

By

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AT the International Symposium on Niamid (nialamide)—1-/2[1]—(benzylcarbamyl) ethyl/2-iso-nicotinoyl hydrazine—a mono-amine oxidase inhibitor, held in Lisbon in November, 1959, T. S. Davies reported that a 35-year-old mongol of imbecile grade, who had previously been inert and who had never spoken, gradually began to speak in monosyllables and, after two months on the drug, was able to converse in short sentences, showed increased physical activity and was able to undertake simple domestic tasks. It is not clear exactly what dosage of Niamid this patient received, but it was within the range of 30 mgm to 75 mgm daily. This report received wide publicity, out of its context, in the lay press, with its inevitable tendency to give the impression that a treatment of mongolism had been discovered, an impression which it is perhaps unnecessary to say Davies had certainly not intended to give.

At the same symposium Rett (2) reported "an increased impulse to motor activity" in mongol children after four to six weeks of treatment with Niamid. Several children started to stand freely by themselves and others to walk. More recently Vasquez (1961) has reported "quickened mental and physical reactions" in mongols after two to three weeks treatment with Niamid. Learning capacity, understanding, speech, and particularly behaviour were significantly improved. However, he noted that these changes were not measurable in terms of elevation of I.Q.

The present clinical trial was undertaken specifically to assess the influence of Niamid on the mental age and behaviour of mongols under more carefully controlled conditions than were possible in Davies' trial. It also formed part, incidentally, of an investigation of the influence of Niamid on the urinary excretion levels of nicotinic acid in a very much larger group of mentally defective patients of all types.

Immediately before the trial, the hospital population of 51 mongols was tested on the Revised Stanford-Binet Intelligence Scale, form 'L'. From these we tried to select patients who could be matched for sex and for ward, to eliminate environmental differences, and for an excess of not more than 10 per cent chronological age and mental age of one member of the pair over the other. This proved possible in ten pairs only, and we accepted for inclusion two pairs in whom the excess was 12 per cent chronological age and two pairs in whom the excess was 16 per cent and 23 per cent mental age respectively. Their chronological ages ranged from 6 years 8 months to 36 years 5 months and their mental ages from 1 year 7 months to 4 years 9 months. One member of each pair was allocated to the Niamid group and the other to the control group on a completely random basis.

The patients in the Niamid group received 1 tablet (25 mgm.) b.d. and those in the control group, 1 inert tablet of identical appearance b.d. from the beginning of the trial.

The active and inert tablets were known to the psychologist and nursing staff only as tablets Nos. 11 and 12 respectively.

At weekly intervals the ward sister completed a seven-point questionnaire (Table I) as to changes in the patient's activity, behaviour, sociability, appetite, sleep, bladder and bowel habits, i.e., whether in these respects there had been improvement, deterioration, increase or decrease or no change, as the case might be, and was also asked to note any other specific changes since the previous report. We purposely avoided a direct question about speech, preferring to leave it to the ward sisters to comment on this in their answers to question 7, if the change was sufficiently noticeable, without any hint from ourselves that we were particularly interested in this aspect of patient activity. Leave and sickness inevitably prevented the questionnaire from being completed by the same ward sister each week, which would obviously have been desirable.

TABLE I

To be completed weekly *Date*.....

NAME..... *Tablets No.*.....

Since taking the above tablets (or since the last report)

1. Has (s)he been	more active less active unchanged?	2. Has his/her behaviour been	better worse unchanged?
3. Has (s)he been	more sociable less sociable unchanged?	4. Has his/her appetite been	bigger smaller unchanged?
5. Has (s)he slept	better worse unchanged?	6. Have his/her bladder and bowel habits been	better worse unchanged?

7. Specify any other changes you have noticed.

Ward..... Charge Nurse/Ward Sister.....

The patients in each group were retested on the same intelligence test 13 weeks from the beginning of the trial. The psychologist reported no appreciable increase in the mental age of children in either group, which could not be accounted for by natural development and, in the case of adults, when the mental age was higher on re-testing than in the immediate pre-trial test, it never exceeded the highest previously recorded mental age for that patient. The psychologist stated that most of the patients were more co-operative during testing, but noted no improvement in speech as regards either fluency or intelligibility.

The results of the pre-trial and repeat intelligence tests (Table II) and the completed questionnaires were submitted to statistical analysis, the statistician being unaware which was the Niamid and which the control group. As one patient (D.C. tablet 12) proved untestable at retesting, he and the patient (R.H. tablet 11) with whom he was matched were excluded from the statistical analysis.

TABLE II

Tab. No.		C.A.	Original M.A.	Original I.Q.	1st re-test M.A.	1st re-test I.Q.	2nd re-test M.A.	2nd re-test I.Q.	Change in months between original and 1st re-test	Change in months between original and 2nd re-test	Change in months between 1st re-test and 2nd re-test
11	R.H.	13·7	1·10	22	1·8	20	1·9	21	−2	−1	+1
12	D.C.	12·4	1·7	19	—	—	—	—	Untestable		
11	A.M.	9·9	1·7	19	1·7	19	1·7	19	0	0	0
12	P.B.	9·10	1·8	20	1·8	20	1·8	20	0	0	0
11	I.F.	7·0	2·3	27	2·3	27	2·4	28	0	+1	+1
12	T.G.	6·8	2·5	29	2·7	31	2·7	31	+2	+2	0
11	A.W.	8·8	1·8	20	1·9	21	1·11	23	+1	+3	+2
12	J.M.	10·6	1·9	21	1·10	22	1·10	22	+1	+1	0
11	E.E.	14·3	4·2	50	4·2	50	4·3	51	0	+1	+1
12	S.R.	14·11	4·1	49	4·2	50	4·1	49	+1	0	−1
11	J.G.	12·7	2·8	32	2·8	32	2·6	30	0	−2	−2
12	L.G.	10·5	2·8	32	3·1	37	3·0	36	+5	+4	−1
11	P.A.	35·9	3·0	36	3·4	40	3·4	40	+4	+4	0
12	D.G.	36·5	2·7	31	2·7	31	2·6	30	0	−1	−1
11	J.P.	18·4	3·4	40	3·6	42	4·0	48	+2	+8	+6
12	D.S..	20·5	3·7	43	3·9	45	3·8	44	+2	+1	−1
11	B.R.	25·1	3·11	47	4·1	49	4·0	48	+2	+1	−1
12	A.K.	26·3	3·11	47	4·7	55	4·4	52	+8	+5	−3
11	D.D.	29·5	4·3	51	4·5	53	3·11	47	+2	−4	−6
12	J.F.	29·9	4·1	49	4·1	49	4·3	51	0	+2	+2
11	M.F.	29·8	3·2	38	3·1	37	3·1	37	−1	−1	0
12	M.S.	28·8	3·4	40	3·2	38	3·2	38	−2	−2	0
11	J.O.	28·4	4·7	55	4·11	59	5·2	62	+4	+7	+3
12	E.R.	30·4	4·9	57	4·11	59	4·11	59	+2	+2	0
11	V.P.	25·11	1·11	23	2·1	25	2·2	26	+2	+3	+1
12	M.W.	25·10	1·10	22	2·0	24	1·11	25	+2	+1	−1
11	E.F.	28·5	2·2	26	2·1	25	2·1	25	−1	−1	0
12	L.A.	28·11	2·8	32	2·9	33	3·1	37	+1	+5	+4

The mean increases in mental age between the two tests were 1·15 months in patients on tablet 11, and 1·85 months in patients on tablet 12, i.e., the mean increase was higher in patients on the control tablets than in those receiving Niamid. However, the difference between the two means, ·70 months, was not statistically significantly greater than zero at the P=·05 level. The answers to questions 1 to 6 in each weekly questionnaire were scored +1 where they indicated improvement, −1 where they indicated a deterioration, and 0 where they indicated no change since the previous report. The total scores on each question for the initial 13 weeks period of the trial of all patients receiving Niamid were compared with the total scores of all patients in the control group and revealed a statistically significant difference, i.e., an improvement, as regards activity and appetite, in the Niamid group and in the same group, a difference, i.e., an improvement, in sociability which was almost statistically significant, but no significant change in behaviour, conduct, sleep, bladder and bowel habits.

In her replies to question 7, i.e., the non-specific question, the ward sister commented on an improvement in speech in one patient (I.F.), C.A. 7·0, M.A. 2·3, after three weeks on tablet 11 (Niamid) and on another (A.W.), C.A. 8·8, M.A. 1·8, that he was starting to talk for the first time after the same length of the same treatment. The former's M.A. was found to be unchanged on re-testing, while the latter's had increased by 1 month.

At the end of the initial period, tablet number 11 was prescribed for those patients who had been receiving tablet number 12, and tablet No. 12 for those who had been receiving tablet No. 11 in the same dosage as before. However, unknown to any but the medical staff and dispenser, the numbering of the Niamid and Control tablets was also reversed at the same time, so that, in fact, each patient continued to receive the same tablets as in the initial period of the trial.

The ward sisters continued to complete the questionnaire at weekly intervals.

The trial was discontinued after a total period of 26 weeks.

Side Effects

One patient developed a mild neutropenia after 20 weeks on Niamid and treatment was discontinued. Her neutrophil count subsequently returned to normal. Treatment was also discontinued in the case of two patients receiving the control tablets—one of whom developed a more severe neutropenia than in the Niamid case and the other of whom was reported as having a reduced platelet count. In both these cases too, the counts returned to normal. No case in either group showed any signs of liver dysfunction nor developed any other obvious side effects.

Results

The psychologist again noted no improvement in speech in any patient. but reported that one patient in the control group was more alert on the second retesting.

The greatest increase in mental age during the trial occurred in an 18-year-old girl (J.P.) in the Niamid group, whose M.A. increased from 3·4 to 4·0 —an increase in I.Q. from 40 to 48. A 28-year-old girl (J.O.) in the same group showed an increase in M.A. from 4·7 to 5·2—an increase in I.Q. from 55 to 62. The largest increases in the control group occurred in the two patients who were excluded from the trial because of the neutropenia already referred to! In one (A.K.), aged 26, the M.A. rose from 3·11 to 4·4—an increase in I.Q. from 47 to 52 (at the end of the initial period it had risen to 55) and in the other (L.A.) aged 29, the M.A. rose from 2·8 to 3·1, an increase in I.Q. from 32 to 37.

On the other hand, the greatest fall in M.A. in the Niamid group occurred in a 29-year-old girl (D.D.) whose M.A. dropped from 4·3 to 3·11—a fall in I.Q. from 51 to 47—at the end of the initial period it had risen to 53. No patient in the control group showed a drop in M.A. of more than two months or a drop in I.Q. of more than 2 points.

The ward sister reported at the end of the trial as follows on the two patients in whom she had reported improvement in speech during the initial 13-week period:—

1. (I.F.) A continued but slow improvement in speech. This patient's M.A. increased by one month during the whole period of the trial—a gain in I.Q. of 1 point.
2. (A.W.) A remarkable initial change in his behaviour—from a boy who who was lethargic, seldom spoke, took little interest in what was going on around him, to a boy who was brighter, took an interest in everything, mixed more and spoke much more frequently. However, during the second period of the trial he partially reverted to his former condition. The patient's M.A. increased by a further two months during the second period—a rise in I.Q. from 20–23 over the whole period of the trial.

The ward sister's reports on two other patients receiving Niamid are worthy of note, as in both, an increase in activity was accompanied by undesirable characteristics—cheekiness and bad language in one case if thwarted in any way, and resistiveness and unmanageability in the other.

Statistical Analysis of the Results of the Complete Trial

Table III

Treatment Group	*Average scores per patient per week* Period 1	Period 2
Activity		
11	+·16	−·01
12	+·01	+·25
Difference (11–12)	+·15*	+·26*
Significant difference	·14	·22
Behaviour		
11	+·15	+·04
12	0	+·24
Difference (11–12)	+·15*	−·20*
Significant difference	·13	·15
Sociability		
11	+·13	+·07
12	0	+·25
Difference (11–12)	+·13	−·18*
Significant difference	·14	·18
Appetite		
11	+·12	+·03
12	+·05	+·18
Difference (11–12)	+·07	−·15*
Significant difference	·13	·14
Sleeping		
11	−·01	+·01
12	−·01	+·01
Difference (11–12)	0	0
(not possible to calculate a valid significant difference)		
Excretory Habits		
11	0	0
12	0	−·01
Difference (11–12)	0	+·01
(not possible to calculate a valid significant difference)		

* indicates that the difference was significantly different from zero at least the P = ·05 level.

The statistician commented as follows: "The treatment effects were different in the two periods. This is obvious from the signs of the differences in the tables above; in period 1, the effects were positive and significant (except for sociability, which was positive and nearly significant), and in period 2 the effects were negative and significant. This looks unrealistic; it could be accounted for by an interchange of treatments when none was intended, or possibly biased reporting on the patients. In any event, it seems unlikely that the patients on treatment 11 would respond fairly definitely in the first period, and hardly respond at all in the second, while those on treatment 12 would respond in the second period and not in the first, and I would hesitate to draw any definite conclusions from these data without further enquiry".

Discussion

A careful check excluded the possibility that the treatments had in fact been interchanged during the second half of the trial as suggested by the statistician, and we were left with the alternative explanation of biased reporting. We have been unable to offer any other likely explanation and although we are

disappointed that the apparent beneficial effects of Niamid were not maintained during the second half of the trial, we are fascinated by this apparent demonstration of the effects of inference and suggestion in influencing the observations and reporting of the nursing staff in two different wards. It seems obvious that they had concluded at the end of the first half of the trial that No. 11 were the active tablets. In any case, had the trial been terminated at the end of the initial period we would have had no reason to suspect the validity of our statistically significant results.*

Conclusion

It is obviously impossible in view of the complete reversal of results on statistical analysis to draw any definite conclusions on the efficacy of Niamid in influencing the mental age and behaviour of Mongols. However, although biased reporting cannot be excluded during the first half of the trial there is no reason to suspect that this would in fact occur until it appeared to the nursing staff that one tablet was definitely more effective than the other.

Acknowledgments

I should like to express my thanks to Dr. J. Jancar for his help in organizing this trial, to the nursing staff for-their ready co-operation in carrying it through, to Miss D. Sperrin West for carrying out the intelligence testing, to Dr. A. I. MacPhail of Messrs. Harvey Pharmaceuticals for arranging the supply of Niamid and control tablets without charge and for Mr. P. R. Avis for undertaking the statistical analysis.

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* The results of the trial during the initial 13 week period were included in a paper by the author which was presented as an interim report at the London Conference on the Scientific Study of Mental Deficiency in July, 1960.