A CONTROLLED TRIAL OF "GERIOPTIL"*

BY

M. D. CASHMAN, M.B., B.S., D.P.M.
Assistant Psychiatrist

AND

T. G. G. LAWES, B.Sc.
Clinical Psychologist

Lancaster Moor Hospital, Lancaster

This paper describes a clinical trial of the effect of "gerioptil" on certain psychological dimensions in a group of senile patients. Gerioptil is the trade name of a preparation which contains Professor Anna Aslan's compound H3 together with a variety of vitamins and vitamin derivatives. It is manufactured by a German drug firm, but is available to hospitals and general practitioners in Britain.

H3 is the name given by Professor Aslan, of the Geriatric Institute in Bucharest, to diethylaminoethyl *para*-aminobenzoate, better known as procaine. This substance has been used for half a century or so as a local anaesthetic, and from time to time for other purposes, including coronary and peripheral vascular disease, allergic states, and rheumatoid arthritis, although for these lesser-known uses it has been superseded by other more efficient or more convenient remedies.

During the last few years, however, a number of papers have appeared, many from Professor Aslan and her colleagues (1959) themselves, advocating the use of H3 in a wide group of disorders, including senility and the physical and psychiatric syndromes seen in association with it.

However, much criticism has been levelled at the clinical reports of these workers, whose papers fall below the standards of statistical method, scientific control, and trial procedure which the modern clinician is entitled to expect from workers making the extensive therapeutic claims that have been advanced by this group. The evidence which Aslan puts forward cannot rival her therapeutic optimism; frequently there are impressive clinical reports and anecdotes, but the use of controls and standardized procedures are not apparent. These criticisms have been the subject of a leading article in the *British Medical Journal* (1959a).

Professor Aslan herself delivered a lecture on H3 in November, 1959, and this has also been reported with considerable criticism in the *British Medical Journal* (1959b).

Accordingly, since with this freely available preparation there appeared to be a discrepancy between the therapeutic claims on the one hand and the acceptable evidence of its value on the other, it seemed suitable to make it the subject of a controlled trial.

Design

Six subjects and six controls were selected at random from a group of 12 elderly women with moderate or advanced senile or arteriosclerotic dementia. Mental deterioration in old people is generally considered to show itself in certain ways. Among these are impairment of memory and of simple learning abilities,

impairment of the ability to perceive and reproduce simple visual patterns accurately, and impairment of intellectual capacities. In contrast, vocabulary is not considered to deteriorate so markedly, and can serve to provide an estimate of premorbid intelligence level.

Selected indices of the above abilities were estimated before the trial. Then the subjects were given first 0.5 ml. of 2% procaine subcutaneously, then 2 ml. of 2% procaine intramuscularly, to obviate the possibility of procaine sensitivity; this was followed by a course of 12 injections of gerioptil H3 intramuscularly over the course of a month as advocated by the makers. The controls were given similar injections of sterile water.

The patients were then reassessed, using the same or parallel test procedures. The test administrator did not know at this stage which patients were members of the experimental group and which of the control group.

Test Procedure

To assess memory and simple learning abilities the two parallel test forms of the Wechsler memory scale were used (Wechsler, 1945; Stone *et al.*, 1946). These forms each contain seven subtests which cover questions on personal and current information, orientation, and other long-term routine memory items; also several simple short-term learning tasks or tests of memory for the immediate past, using numbers, stories, and also simple diagrams and word associations. The form administered first to any patient was determined by chance, using a list of random numbers. The alternative form was then used later for reassessment. The rules for scoring as well as for administration of every item in these tests are quite specific and precise. Improvement or deterioration in memory and learning ability was determined by comparison of raw scores and subtests. On the full scales the total score is corrected for age by the addition of an appropriate constant to give a so-called memory quotient, but differences in total raw scores and differences in memory quotient are obviously the same.

The Bender gestalt test of figure-drawing (Bender, 1938) was used to assess ability to perceive and reproduce simple visual patterns. No time limit is involved, and all that is required is to copy a few apparently simple geometric figures. With any one of these, however, certain key theoretical components of sensorimotor organization must be in operation, otherwise there is a tendency for the figure to be changed and reorganized in the drawing. Impairment of ability or immaturity of development can be identified from the drawing produced, which may be given a mental-age score. There are no parallel forms for this test, and the same figures were therefore used for retesting.

Intellectual capacity was tested by the simpler coloured version of Raven's (1956) Progressive Matrices, using the norms he has published for old people (Raven, 1958a). Ability on this test is severely diminished in senile dementia. For retesting, the identical test was used again, as no parallel form exists.

Finally, to estimate premorbid intelligence level, the Mill Hill vocabulary definitions scale was used. Two equivalent lists of words are contained in the full test, and these were used separately as parallel forms, the scores obtained on each occasion being pro-rated to obtain the total score. Raven's (1958b) norms for old people on this test explicitly contrast and compare it in detail with his coloured progressive matrices.

*Based on a paper read at a meeting of the Manchester Regional Psychiatric Association at Lancaster Moor Hospital on June 29, 1960.

Results

After retesting, raw scores were compared on each test and subtest, and each patient was placed in one of three categories, "improved," "no change," or "deteriorated," for that particular function. On the complete battery of tests, including the Mill Hill vocabulary definitions scale, each patient was also given an overall rating signifying change in one direction or the other.

According to the claims made for geriopitil, the hypothesis expected to be supported by the results is that all those patients who were treated with this preparation would improve, while those who did not receive it would continue to deteriorate in accordance with the natural course of the disease, as in Table I, Hypothesis I.

Allowing for the effects of extraneous factors, it would still be supposed that those treated with geriopitil would show an improvement as a group when compared with those not so treated; such a modification of the basic hypothesis is shown in Table I, Hypothesis II. Moreover, since the claims made for geriopitil are quite extensive, not only an overall improvement would be expected, but also an improvement in each mental function assessed, or at least in one or two of them.

Such hypotheses, however, are not compatible with the results. Overall, four out of six patients who had treatment deteriorated, while five out of six untreated patients improved; these results are shown in Table I. Also in Table I are the results for each separate test, and these show that there was no improvement in any one of the mental functions assessed. The results for individuals are shown in Table II.

The memory of all the subjects treated with geriopitil and the intellectual capacity of half of them deteriorated; and this was the pattern of the findings throughout all seven subtests of the memory scale, with the exception of only one. This exception was memory for design, in which the experimental group showed a slightly greater improvement than the control. In one other, personal and current information, subjects tied with controls;

while in the remaining five, orientation, mental control, logical memory for stories, digit span, and associate learning, the results in the control group were more favourable by comparison. In the Bender gestalt figure-drawing test, although the results were not so markedly against geriopitil, they still provided no evidence in its favour.

Even the Mill Hill vocabulary definitions scale weighs against geriopitil, although assessing a mental capacity supposedly less affected by dementia than are the other psychological indices. On this test, four out of six patients who received geriopitil did not score so highly on the second occasion, whereas four out of six patients who did not receive the treatment improved in their scores.

Conclusions and Discussion

Although the numbers concerned have been far too small for statistical computation, nevertheless the results suggest quite clearly that those patients who did not receive the course of treatment had the natural progression of their disease retarded to some extent, while those who were treated with geriopitil deteriorated still further. In fact, an effect contrary to the claims made for geriopitil seemed to have occurred, and this trend is reflected in almost every part of each test taken separately.

Both subjects and controls had other treatment in the form of sedatives, hypnotics, and tranquillizers during the trial, but, whereas this was necessary for their own welfare and comfort, it should not be expected to interfere with any effect on the intellectual dimensions under review; nor was any treatment given which is listed as contraindicated during geriopitil therapy by the makers.

The limitation in the number of subjects in the trial was necessary in view of the very laborious and time-consuming nature of these psychological estimations in demented patients, since one of us (T. G. G. L.) had to spend in all something of the order of six to seven hours with each patient, while continuing other research work and routine clinical work as well. This points to the possibility of increasing the number of subjects and controls but limiting the extent of the formal intellectual assessment in a future trial.

The reliabilities and validities of some of the tests used in this study have been called in question. Hall (1957), for example, examined the reliabilities and correlations with intelligence of the Wechsler memory scales, using a group of young adult, non-organic, psychiatric patients. She found the internal consistency of the subtests generally low, and their correlations with intelligence high, so that she queried the uniqueness of the contribution the Wechsler memory scale could give to studies of human behaviour. Wechsler (1960) has emphasized that neither of his memory scales has been very thoroughly standardized, and that they were intended primarily as clinical instruments. Inglis *et al.* (1956) concluded that memory function was not particularly useful in the differential diagnosis between elderly psychiatric patients having disorders of functional and organic origin respectively. On the basis of their results they suggest that the Bender gestalt test gives a more valid contribution to the required criterion. On the other hand, their evidence does point to the existence in their patients (after the influence of intelligence on the subtests has been computed and removed by the technique of partial correlation) of some such thing as "memory function."

TABLE I

	Overall Changes		Memory		Figure Drawing		Intellectual Capacity		Vocabulary		Hypothesis I		Hypothesis II	
	G	P	G	P	G	P	G	P	G	P	G	P	G	P
Improved ..	1	5	0	4	3	4	2	3	2	4	6	0	3	1
No change ..	1	0	0	1	1	1	0	1	2	0	0	0	2	2
Deteriorated ..	4	1	6	1	2	0	3	1	4	1	0	6	1	3

G=Gerioptil. P=Placebo.

TABLE II

Patient	Age	Memory Scale Raw Scores		Mean Figure Drawing Age Levels (in Years)		Coloured Progressive Matrices Scores		Mill Hill Vocabulary Scores		Over-all Trend
		I	F	I	F	I	F	I	F	
Gerioptil Group										
A	64	4	0	3	4	0	0	14	0	—
B	76	9	6	3	4	14	0	33	22	—
C	75	19	11	5	4	7	6	45	39	—
D	81	15	5	3	4	11	9	53	58	0
E	75	41	37	8½	8	14	19	63	62	—
F	75	42	35	8	8	23	27	53	57	+
Control Group										
G	79	25	14	4½	6	12	14	39	42	+
H	76	30	43	8	7½	18	23	44	44	+
I	73	0	7	3	5	13	13	42	48	+
J	84	12	12	7	6	14	9	42	45	+
K	79	0	8	3	4	7	7	27	26	—
L	71	8	16	3	5	7	11	36	49	+

I=Initial. F=Final. +=Improved. 0=No change. —=Deteriorated.

Notwithstanding these remarks, in the absence of any other data, the results obtained in this trial cast very grave doubts upon the claims made for the preparation used.

Summary

A small controlled trial has been carried out with six subjects and six controls of the effect of "geriopil H3" on the mental ability, as measured by a number of psychological tests, of patients with senile or arteriosclerotic dementia. The trial has failed to prove that geriopil is of any value in this respect.

REFERENCES

- Aslan, A., *et al.* (1959). *Research on Novocain Therapy in Old Age*. Consultants Bureau Inc. Translation of papers from *Die Therapiewoch.* 1956-1957.
Bender, L. (1938). *A Visual Motor Gestalt Test and its Clinical Use*, edited by L. G. Lowrey. Amer. Orthopsychiat. Ass., New York.
Brit. med. J., 1959a, 2, 1163.
— 1959b, 2, 1175.
Hall, J. C. (1957). *J. cons. Psychol.*, 21, 131.
Inglis, J., Shapiro, M. B., and Post, F. (1956). *J. ment. Sci.*, 102, 589.
Raven, J. C. (1956). *Coloured Progressive Matrices Revised Order*. Lewis, London.
— (1958a). *Guide to Using the Coloured Progressive Matrices Reprinted with Norms for Old People*. Lewis, London.
— (1958b). *Guide to Using the Mill Hill Vocabulary Scale with the Progressive Matrices Scale*, revised. Lewis, London.
Stone, C. P., Girdner, J., and Albrecht, R. (1946). *J. Psychol.*, 22, 199.
Wechsler, D. (1945). *Ibid.*, 19, 87.
— (1960). Personal communication (letter to T. G. G. Lawes).

RESPIRATORY PARALYSIS AFTER A LARGE DOSE OF STREPTOMYCIN

REPORT OF A CASE

BY

G. C. FISK, M.A., B.M., F.F.A.R.C.S.
F.F.A.R.C.S.

Registrar, Department of Anaesthetics, Guy's Hospital,
London

A number of cases have been reported in which intraperitoneal administration of neomycin in large dosage has been followed by the development of post-operative respiratory insufficiency or apnoea (Pridgen, 1956; Poth, 1957; Middleton *et al.*, 1957; Engel and Denson, 1957; Ferrara and Phillips, 1957). Streptomycin has been shown to be capable of blocking neuromuscular conduction in experimental animals (Brazil and Corrado, 1957; Bezzi and Gessa, 1959), and in human intercostal nerve-muscle preparations (Sabawala and Dillon, 1959). Loder and Walker (1959) have reported three cases of muscular weakness and visual difficulty, resembling a myasthenic state, in patients receiving standard intramuscular doses of streptomycin. The symptoms were relieved by neostigmine and by withdrawing the streptomycin.

Streptomycin is not infrequently instilled into the peritoneal or pleural cavity at the end of some surgical procedures, and Bush (1961) has described the occurrence of prolonged post-operative apnoea in a child aged 6 months, which he attributes to neuromuscular blockade by the combination of D-tubocurarine and a large dose of streptomycin (1 g. intraperitoneally). I feel that a similar case occurring in an adult is worth reporting.

Case Report

The patient, a fit man aged 53, had a stricture of the lower end of his oesophagus. An oesophageal hiatus hernia had been repaired nine weeks previously, when he was noted to be somewhat resistant to anaesthetic drugs. His weight

was 12 st. (76.2 kg.), haemoglobin 13.8 g./100 ml., and blood pressure 135/80 mm. Hg; he was classed as a good risk for anaesthesia and surgery. The proposed operation was an ileocaecal transplant and anastomosis for relief of the oesophageal stricture.

Premedication with papaveretum 20 mg. and scopolamine 0.4 mg. was given at 8 a.m. At 9 a.m. thiopentone 0.4 g. and then suxamethonium 50 mg. were given intravenously, the lungs were inflated with oxygen, and 2 ml. of 5% cocaine solution was instilled into the trachea, followed by intubation with a No. 10 cuffed Magill tube.

Operative Course

When the ileocaecal transplant had been mobilized and anastomosis with the oesophagus started, its blood supply was found to be inadequate. The ileocaecal transplant was therefore resected and replaced by jejunum, the whole procedure lasting seven hours. The patient was resistant to the drugs used, and a total of 87 mg. of D-tubocurarine and 170 mg. of pethidine, and a further 0.2 g. of thiopentone, were required to control "bucking" and straining. He was ventilated throughout with nitrous oxide and oxygen, by the Blease pulmoflator or by hand through a Waters canister. The blood-pressure was steady at about 110 mm. Hg systolic except for a short period when it fell to 90 mm. Hg, when 9 mg. of methylamphetamine was given. The blood loss, measured by weighing the swabs and adding to the loss via suction, was 1,030 ml., and 1,500 ml. of whole blood was replaced together with 1 g. of calcium gluconate. Before the wound was closed a total of 10 g. of streptomycin powder was administered, 5 g. being placed in the peritoneal and 5 g. in the pleural cavity. Spontaneous respiratory movements began during closure, after which atropine 1.2 mg. and then neostigmine 2.5 mg. were given intravenously. The patient left the theatre at 4 p.m., when his general condition was satisfactory, his blood-pressure being 110 mm. Hg systolic, and respiratory function appeared adequate.

On the way back to the ward, respiratory movements diminished greatly over a period of two to three minutes, becoming very shallow. The patient was rapidly returned to the theatre, reintubated, and ventilated with oxygen. The state of his circulation was quite satisfactory at this time, blood-pressure being unaltered. Atropine 0.6 mg. intravenously, followed by two doses of 1.25 mg. of neostigmine, resulted in a marked improvement in spontaneous ventilation, which lasted for less than a minute on each occasion. 2 ml. of nikethamide had no effect. At this stage the blood-pressure fell abruptly and became unrecordable. Intravenous methylamphetamine 30 mg. brought the pressure up to 70 mm. Hg. Additional blood was transfused and hydrocortisone 100 mg. given intravenously. Soon after this the blood-pressure was 120 mm. Hg and his cardiovascular state caused no further anxiety.

Respiratory movements were still very feeble, and the patient was therefore connected to a Barnet ventilator and inflated with oxygen. After a few minutes, assistance by means of the patient-triggering device was sufficient. This was necessary for another hour, during which he became responsive to commands to move his eyelids and head. Towards the end of this time he was able to open his eyes and wrinkle his forehead. At this stage the ventilator was disconnected and he breathed air through the endotracheal tube with no cyanosis, although there was still some tracheal tug and mild ptosis with a "myasthenic facies." Forty minutes later the endotracheal tube was removed. Ventilation was adequate, with only slight tracheal tug and facial weakness. The patient now complained of pain from the incision, and papaveretum 10 mg. was given subcutaneously, with some relief of pain but no adverse respiratory effect. He was finally returned to the ward in a satisfactory condition at 6.30 p.m., and made an uneventful recovery, having no recollection of the events in the immediate post-operative period. However, for some days afterwards he was subject to undefined frightening dreams, and said that he felt a little afraid of falling asleep in case he did not wake up.