

THE RESULTS OF THE EXPERIMENTAL  
ADMINISTRATION OF AMPHETAMINE SULPHATE  
IN OLIGOPHRENIA

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A NUMBER of drugs have been employed in an attempt to increase the mental capacity of oligophrenics. The effect of thiamine on learning demonstrated by Harrell (1943, 1946) led Rudolf (1949, 1950) to use this vitamin in the treatment of oligophrenia. Similarly, the early studies of Zimmermann and Ross (1944) on glutamic acid resulted in a large number of papers on its debatable effect in feeble-mindedness (Zimmermann, Burgomeister and Putnam, 1946, 1947, 1948; McCulloch, 1950; Ellson, Fuller and Urmston, 1950; Quinn and Durling, 1950; Lafon, Faure and Bascou, 1952; Oldfelt, 1952). The results of *celastrus paniculata* on mental defectives have been described by us elsewhere (Morris, MacGillivray and Mathieson, 1953, 1954).

Amphetamine ("benzedrine",  $\beta$ -phenylisopropylamine) is a sympathomimetic amine resembling ephedrine and adrenaline, but differing chiefly in its greater abilities to stimulate the higher centres of the nervous system and particularly the cerebral cortex. This mechanism of cerebral stimulation has not been fully elucidated. Blaschko (1940) suggested that the ability of the sympathomimetic amines to act as analeptics can be directly correlated with this ability to inhibit amine oxidase in vitro. Mann and Quastel (1940) found the respiration of brain tissue to be inhibited by certain amines such as tyramine and isoamyline which are oxidized to ammonia and their corresponding aldehydes by amine oxidase. The addition of benzedrine increases oxygen consumption by the brain by binding amine oxidase so that toxic aldehydes cannot be liberated. However, amphetamine cannot increase the respiration of brain inhibited by anaesthetics or produce an increased oxygen consumption by normal brain tissue. It is doubtful whether the peripheral effects of amphetamine on adrenergic structures can be linked with the excitatory effects on the central nervous system.

The effects of amphetamine on the central nervous system have been summarized by Wilson and Schild (1952) as follows. The diffident individual becomes more confident, with greater capacity to make decisions and his thought

processes are speeded up. This is often shown in an increased facility by the patient to express himself in speech. Although the capacity to do simple additions is increased, there is less effect on the ability to concentrate, and some subjects find themselves slower in solving more complicated problems which demand concentration. Amphetamine does not increase the efficiency of work; Browne (1947) observed that if the drug was given to fatigued pilots it made them feel better, but their performance did not improve and if the job was difficult their performance in fact deteriorated.

The euphoric action of amphetamine was first recorded by Peoples and Guttman (1936) while experimenting on its action in raising the blood pressure. Subsequently Guttman and Sargant (1937) reported their work on 250 patients and controls at the Maudsley Hospital. They found an increased confidence, increased initiative and increased ease of making decisions, while the patients became more talkative. Some subjects became restless, and vasolabile persons tended to complain of dizziness, shivering, palpitations, tremor or anorexia. There is considerable individual variation in the response to these sympathomimetic amines. Further early descriptions of the psychic results of amphetamine are those of Myerson (1936), Davidoff and Reifstein (1937), Nathanson (1937), Fisher (1937), Bahnsen, Jacobsen and Thesleff (1938) and Jacobsen (1939).

Increased mental performance by actual objective measurements has also been described by some workers. This was first suggested by Sargant and Blackburn (1936) who investigated the results of amphetamine on 48 adult mental hospital patients, using Cattell's intelligence tests, and reported an 8 per cent. improvement in test scores. The results reported in this paper were not statistically significant and can be largely discounted for this reason. Subsequently, Molitch and Eccles (1937) studied the effect of amphetamine on children's intelligence scores. Ninety-three boys between the ages of eleven and seventeen of varying mental levels were tested at intervals before and after a placebo or amphetamine was ingested. It was noted that both groups improved their scores, but the children tested after amphetamine exhibited a greater improvement than those taking the placebo. The tests used were the measuring of hand grip by the Smedley dynamometer, the Witmer formboard, a memory-for-design test and three standardized verbal intelligence tests, i.e. the Kent E.G.Y., the Morgan intelligence test and the Kuhlman-Anderson intelligence test. The Kleemeiers (1947), in an interesting experiment, took as their subjects twenty-seven intelligent university students. These were given glucose and amphetamine alternately and it was found that all speed tests showed an increase in "t" score, that is, the ratio of the difference between means to its standard error. The testees showed increased performance with amphetamine on a number of timed tests and this they believed to be due to an increased flexibility. There was no differential effect on fast and slow workers. Performance was apparently readily facilitated on the multiplication, selective substitution and arithmetic speed tests used in this study. Facilitation was also noted on the letter series, paper and pencil, motor over and under, and word completion tests, but these cannot be accepted as being highly reliable.

Hill (1947) points out that the improved performance which has been reported on intelligence scores under the influence of amphetamine is due to increased motor and speech activity, i.e. a change in the executive rather than in the affective elements of the mind. This, he states, occurs in normal people, mental patients and in children. Rudolf (1947) believes that relief of fatigue may account for the increase in the scores, and emphasizes that this is particularly

likely in those patients reported by Sargant and Blackburn (1936), as these were psychopaths who are known to be especially liable to fatigue.

The use of amphetamine in the treatment of behaviour problems in children has been discussed by Lindsley and Henry (1942). They noted a great improvement in behaviour in such cases but the electroencephalograms were unaltered. The explanation of this according to Walter (1950) is that in these children certain cerebral functions have developed unusually slowly and the child is faced with an environment which he is not yet able to tolerate and manipulate in a reasonable way. Most of these children are not able to exploit any particular ability, and resort to sulkiness, defiance of authority or violence in an attempt to alter their surroundings. For such children amphetamine provides a substitute for the natural brilliance of the better endowed child by enhancing their interest and perhaps their ability. The drug cannot instantly accelerate the development of the cortico-basal mechanisms, so that the theta activity in the EEG persists, but it does seem able to stimulate those activities which are already mature.

The results of amphetamine sulphate on the EEG in the normal person are unspectacular, as might be expected. Corresponding presumably to the increased alertness and psychic activity is a modification of the cortical frequencies similar to that accompanying the change from rest to attention. This was shown with the aid of the Grass frequency analyser by Gibbs and Maltby (1943) who gave 20 milligrams of the drug intravenously. 10 milligrams of the sulphate produce no detectable change in the unanalysed EEG (Gibbs, Gibbs and Lennox, 1937; Blake, Gerard and Kleitman, 1939). Sleep tends to be lighter after amphetamine sulphate, and the delta activity is reduced in voltage and amount (Blake *et al.*, 1939). Although amphetamine is a powerful vasoconstrictor it apparently does not reduce the cerebral blood flow (Schmidt, 1944).

The effects of amphetamine on mentally deficient children have received little attention. The work of Bradley (1937) who found that administration of the drug tended to improve school performance, particularly arithmetic, in one half of the children treated, led Cutler, Little and Strauss (1940) to investigate the results of the drug on oligophrenics. They approached the question from two angles; the first problem being to assess the effect of a small daily dose of amphetamine over a protracted period on the capacities of mentally defective children, which might be measured by psychometric tests; the second to determine whether gain would appear in psychologically measurable skills when a relatively high dosage of amphetamine was administered only once to children of like intelligence. They concluded that medication in small doses did not show much if any significant effect on the mental reaction of defective children as measured by the Stanford and Terman Merrill Form M Revision of the Binet, the Grace Arthur Point Performance Scale, the New Stanford Achievement Test, the Vineland Social Maturity Scale and by tapping and cancellation tests. The stimulation given by amphetamine did not measurably improve test achievement immediately after administration or subsequent to a period of six months after medication had been withdrawn. There were no changes in behaviour, either favourable or unfavourable, to be observed in the group which received amphetamine in small doses as compared with the matched group of controls. It was noted that amphetamine given as a sudden stimulant affected favourably the outcome of the following tests—Tapping, Porteous Mazes, Knox Cubes, Seguin and Ferguson Form Boards and Healy II Picture Completion. It was concluded that these results were explained by

amphetamine stimulating particularly psychomotor activity which is involved to a greater extent in these performance tests. They observed further, that amphetamine tended to affect the utilization of learned material in academic fields as shown in the New Stanford Achievement Test. A similar improvement in normal boys on the Stanford Achievement Test was reported by Molitch and Sullivan (1937). Moskowitz (1941), in an essentially clinical study, points out that in selected cases of uncomplicated oligophrenia, prolonged administration of amphetamine sulphate raises the ability of the central nervous system of the mentally handicapped to the point where educational training can be utilized, resulting in a greater performance ability. He suggests that the selection of these cases can be correlated with somatic factors, body measurements and response to adrenaline injection.

In view of the comparative paucity of the literature concerning the action of the drug on mental defectives it was decided to set up a carefully controlled investigation on the clinical action and psychological effects of the drug on a group of institutionalized oligophrenics.

#### *Selection of Groups to be Tested*

Patients in the hospital group were surveyed and a total of fifty were selected with an age range of 15½ to 32 years and intelligence quotients from 60 to 74. Epileptics and post-encephalitics were excluded as also were those with known psychopathic tendencies or subject to emotional or other stress from friends or relatives. Some subjects who had been used in previous experiments in relation to *celastrus paniculata* were included, but only in the control group. Two groups were then formed, matched for age and intelligence quotient, the experimental group of eleven males and fourteen females with an average intelligence quotient of 66 on the Terman Merrill scale and an average age of 22·5/12 years, and the control group of twelve males and thirteen females who had an average intelligence quotient of 66 on the same scale and an average age of 22·5/12 years.

The following test battery was employed in the experiment:

Terman Merrill Revision of the Binet Scale, Form L or M, before and after administration.

Cattell's Non-Verbal Intelligence Scale I, Form A before and Form B after administration.

Kohs' Block Designs before and after administration.

#### *Tests of Learning*

- (1) Verbal Paired Associates. The test consisted of a list of numbers associated with animals, the names of the animals corresponding to the numbers being recalled after one trial.
- (2) Non-Verbal Paired Associates. Coloured cards were matched with designated shapes of openings in a box. This, like the preceding test, was scored for time and for the number of prompts required before two correct performances.
- (3) Number Sorting. Numbered cards were placed in irregularly distributed matching compartments in a box, the results being scored for speed and accuracy.

#### *Tests of Voluntary Attention*

- (1) Number Cancellation. A sheet of numbers in irregular order from 0-9 was given to the candidate who struck out a stated number. The score was based on the number of cancellations made in 90 seconds.

- (2) Linking Circles, as in the Kleemeiers' experiment (1947), where testees linked circles set out in irregular horizontal pattern interspersed with X's, before administration; on retest the figures 1 and 2 were substituted respectively. Scores were calculated on speed and accuracy over a period of 90 seconds.
- (3) An L's test similar to the G.A.T.B. Test, where the letter was marked by the examinee. Results were scored for speed and accuracy.
- (4) The number of X's made in a minute.
- (5) Arithmetic. Ungraded sums in addition were scored for the number completed and the number of errors.
- (6) Fluency. Verbal enumeration and scoring of "the number of things that can be bought" and on retest "the number of things that one can see" in a minute.

#### *Memory*

- (1) Visual apprehension was tested by five-second exposures of three sets of groups of ten common objects. Points were given for accuracy. Inaccuracies were measured by the number of articles falsely recalled.
- (2) Memory for Design. Geometrical shapes were reproduced from memory from two cards of nine drawings, each exposed for fifteen seconds. Scoring was computed on correct placing and accuracy.

#### *Level of Aspiration Test*

The number of taps per minute made by the examinee with a Morse key were measured by an impulse counter. The three ratings were: the number of taps; judgment discrepancy score based on the difference between actual performance score and judgment score on trial X, underestimation of past performance giving a negative score, overestimation a positive one; goal discrepancy score based on the difference between actual performance on trial X and aspiration for trial X+1.

The same examiner gave the group tests before and after administration, the same procedure being followed in the case of the individual tests. Closely parallel tests were substituted after administration.

#### *Administration*

By courtesy of the makers a supply of identical dummy tablets containing an inert substance (lactose) was provided and the daily dosage of amphetamine and the placebo was arranged as follows—5 mg. for the first week, 10 mg. for the second week, 15 mg. for the third and fourth weeks, the latter dosage being continued until testing was completed.

During this period the experimental and control groups were weighed weekly, their sleep records surveyed and their behaviour observed by skilled nursing staff for any variation in either behaviour or working capacity. The side effects of the drug were the subject of enquiry and the evidence of any was reported. The nursing staff concerned were unaware which tablets consisted of placebo.

#### *Intelligence Test Results*

After administration both groups showed similar slight improvements in their scores on the three intelligence tests. The changes were exceedingly small on the Cattell Scale being less than one point of average I.Q. in either group, a consistency which contrasts strikingly with results reported on this test in a previous experiment (Sargant and Blackburn, 1936). The preliminary and post-treatment ratings on Kohs' Block Design test showed the high positive corre-

lation of .95 in the control group and .93 in the experimental group. On the Terman Merrill Scale there was an average improvement of four I.Q. points in either group, this may be partly due to familiarity with the test which is in current use in this hospital group, but the change is insignificant and comparable with those reported in previous experiments, e.g. (Cutler *et al.*, 1940). The mean intercorrelation of the three preliminary test scores of the whole group was relatively low, being +.47.

The results indicate no improvement in intelligence due to administration and in fact the control group average improvement on each test was slightly greater than that of the experimental group.

#### *Tests of Learning*

On the verbal paired associates retest both groups shortened their learning time and reduced the number of prompts required after administration, the control group improving slightly more than the experimental group. Scores were satisfactorily distributed, the difference between the groups was insignificant and practice effect was slight.

On the non-verbal paired associates test there was a statistically significant reduction in the number of prompts needed by the control group in the retest, as compared with the experimental group. This is largely due to the major improvements in the scores of four patients. It indicates the risk of obtaining superficially misleading results even in carefully controlled experiments. The control group also learned more quickly on the retest than the experimental group but the difference in this case was not significant.

Both groups took approximately twice as long to establish seven verbal associations as they did eight visual associations. In view of the testee's limited range of intelligence there were wide variations in the learning times of both groups. On the verbal test initial learning times ranged from 27 seconds to 34 minutes 47 seconds and on the non-verbal test from 25 seconds to 16 minutes 7 seconds.

In the number sorting test both groups showed practice effect, being initially quicker, but after administration they reduced their time proportionately less over five trials. This was due to their improvements bringing them nearer to the minimum time required to place the cards in the compartments.

#### *Tests of Sustained Voluntary Attention*

The majority of patients in both groups showed slight improvements after administration, attributable to practice effect.

In the number cancellation test the gains were similar in the two groups, but in linking circles, statistical analysis revealed that the improvements in the scores of the experimental group were significantly greater than those of the control group, these gains were also satisfactorily distributed. The experimental group made more errors on the retest than did the control group, but this difference was not significant. The retest results of both groups on the L's test and on the X's in a minute test also showed similar minor increases.

The Arithmetic test results of the two groups were essentially the same before and after administration but the experimental group increased their errors slightly more than the control group. This stability in the level of performance is also in contrast to gains reported in previous experiments. There was no significant change in verbal fluency in either group.

*Tests of Memory and Apprehension*

The average span of visual apprehension of common objects was almost identical in the two groups, namely five out of ten objects in fifteen seconds exposure, and remained essentially unchanged after administration. Both groups reduced the number of false recollections on the retest, the experimental group making a greater reduction than the control group contrary to what might have been expected.

In the recall of designs from memory the control group average score increased very slightly more than that of the experimental group but the experimental group attempted rather more drawings than the controls after administration. The difference was not statistically significant. Both groups recalled approximately half the nine designs on each card, scored for placing and accuracy.

*Level of Aspiration Test*

There was little change in the number of taps made after administration and the averages of the two groups were closely similar.

In predicting their future score the experimental group was slightly more ambitious than the control group. At the first testing both groups showed some optimism. After administration the average goal discrepancy of both groups was less, being nearer their last actual score. This conservative tendency was slightly greater in the case of the experimental group, a fact which seems to contraindicate euphoria. Both groups tended to under-estimate their past performance on the first testing and a similar trend was evident after administration although it was less marked in both groups.

The general aspect of the test results indicates little difference between the number of improvements in the scores of the two groups, such as were found, being within the limits of chance variation. On a total of 650 ratings, the experimental group showed 361 improvements against 348 in the control group. It is of interest that these improvements were normally distributed among the members of both groups, the average number in the experimental group being 14.4 with a range of 8 to 21 against an average of 14.0 with a range of 8 to 19 in the controls out of a total of 26 ratings. The improvements found were insignificantly small and only three of the experimental group and two of the control group showed more than four marked improvements on individual tests.

The "t" scores showed a significant difference between the improvements of the groups in only two instances. The experimental group improved more than the control group in linking circles and the control group required significantly fewer prompts in the re-test of the Non-Verbal Paired Associates. The control group showed a very slightly greater but not significant improvement compared with the experimental group in seventeen of the remaining twenty-four ratings.

*Physical and Mental Condition*

All patients were weighed weekly during the experiment and at the conclusion of treatment the experimental group had lost an average of two pounds in weight while the control group were unchanged on average. In the experimental group nausea was noted in one male and two female patients, while a hypomanic state with restlessness and aggression was reported in three cases, who comprised the most psychologically immature and emotionally labile members of the group. No other toxic effects were observed. Three other cases

were improved in working capacity and interpersonal relationships. In the control group no behaviour changes were noted beyond a phase of aggression in one patient for a brief period due, we understand, to a family quarrel.

	Scores						"t" Score
	Experimental Group			Control Group			
	Before	After	Improvement	Before	After	Improvement	
Terman Merrill. I.Q. . . . .	65.5	69.4	3.9	66.3	70.7	4.4	-.57
Cattell. I.Q. . . . .	61.0	61.3	0.3	64.7	65.3	0.6	-.18
Kohs' Blocks. Mental age in years	9.11/12	10.4/12	5/12	10.5/12	11.8/12	1.3/12	-.51
Verbal Paired Associates:							
A. Time . . . . .	7' 29"	7' 17"	+12"	6' 56"	5' 49"	1' 7"	-.40
B. Number of prompts . . . . .	18.4	18.4	0	20.4	16.5	3.9	-.91
Non-Verbal Paired Associates							
A. Time . . . . .	3' 4"	3' 52"	-48"	4' 34"	2' 53"	+1' 41"	-1.72
B. Number of prompts . . . . .	17.0	19.4	-2.4	31.3	17.5	13.8	-2.16
Number Sorting:							
Times for first trial (in seconds)	35.4	26.9	8.5	33.7	25.0	8.7	-.05
Percentage of improvement on fifth trial . . . . .	33.1	26.4	-6.8	37.7	26.4	-11.3	+ .64
Number Cancellation . . . . .	36.5	46.3	9.8	39.3	49.1	9.8	-.01
Linking Circles . . . . .	33.6	43.3	9.7	44.3	46.6	2.3	+2.38
L's test . . . . .	48.8	56.2	7.4	49.4	57.6	8.2	-.02
X's in one minute . . . . .	81.6	86.7	5.1	84.0	87.9	3.9	+ .28
Arithmetic . . . . .	36.0	36.6	0.6	35.8	37.7	1.9	-.73
Fluency . . . . .	19.1	19.1	0	23.8	24.1	0.3	-.33
Visual Apprehension . . . . .	15.8	16.4	0.6	15.8	17.2	1.4	-1.06
Memory for design . . . . .	18.4	19.0	0.6	20.2	20.9	0.7	-.06
Level of Aspiration:							
Number of taps . . . . .	76.2	81.0	4.8	73.2	78.0	4.8	+ .02
Goal discrepancy . . . . .	+2.5	+0.6	-1.9	+1.5	+0.1	-1.4	-.15
Judgment discrepancy . . . . .	-6.8	-4.2	+2.6	-5.5	-2.3	+3.2	-.31

#### DISCUSSION

In our experiment no improvement was found in testing intelligence on the Terman Merrill Scale just as Cutler *et al.* (1940) reported only a few small insignificant improvements on the same scale. On the other hand these authors found improvement in the performance tests, due, they suggest, to increased psychomotor activity with sudden administration of the drug. This result is at variance with our experience with prolonged administration where no increased psychomotor activity was noted for example in the Kohs' Block Design Test. Similarly, the scores on the tapping part of our level of aspiration test did not show the improvement reported by these authors. In fairness, it should be stated that their results were based on sudden medication and where prolonged administration was tried, their results were similar to ours. The same applies to number cancellation tests. Apparently the results of these observers were not subjected to statistical analysis.

The results obtained in this experiment compare unfavourably with the claims made by Moskowitz (1941) but he employed a larger dosage coupled with thyroid medication in an essentially clinical study.

Sargant and Blackburn's (1936) findings were based on a study of a group of adult patients in a mental hospital and have already been subject to criticism by Rudolf (1947) who emphasized that the relief of fatigue resulted in increased test scores and postulated that psychopaths show undue proneness to fatigue. In our experiment no change was found on Cattell's Scale; it may be because our testees were functioning at a lower level of mental capacity.

In the linking circles test there was a barely significant increase in the score of the experimental group. This apparent increase was not to be found in other tests involving essentially the same abilities. In our mental defective group we were unable to confirm the claims made by many authors that improvement in arithmetical ability resulted from administration of the drug. Both speed and accuracy were measured and showed no change.



Other investigators who have reported euphoria in normal adults, children and mental hospital patients, have generally based their findings on subjective reports from the patients themselves. It must be generally agreed that the drug does produce euphoria in non-defective patients. Neither Cutler *et al.* (1940) nor Moskowitz (1941) mention euphoria in their experiments, an experience which is paralleled in this study where neither clinically nor in the test used for the level of aspiration was there any evidence of this symptom.

Two previous experiments conducted on patients of this hospital group have resulted in a considerable degree of sophistication in relation to the results of the administration of various drugs. Therefore it is submitted that the traditional suggestibility of the mental defective was probably not a potent factor contributing to the results.

#### CONCLUSIONS

It is apparent that treatment with amphetamine does not increase intelligence, learning capacity, speed and accuracy of voluntary attention, fluency or memory in mental defectives.

The results of this study do not support the contention that the administration of amphetamine can raise the ability of the central nervous system of the mentally handicapped to the point where educational training can be utilized.

It is of considerable interest that this defective group did not experience the customary euphoria which the drug is so well known to produce.

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