

THE TREATMENT OF MENTAL DEFECTIVES WITH THIAMINE.

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THIAMINE or aneurine has for many years been known as the anti-neuritic vitamin, although action of this substance in organic nervous trouble is not established. Less well-known is its action on the higher cerebral processes, but results of investigations appear to show that it has a definite effect on these. M. V. Dias (1947) found that the application of thiamine hydrochloride solution to the motor cortex of unanaesthetized dogs produced clonic contractions of the appropriate muscles, and Harrell (1946) reports striking psychological results on normal children.

OTHER SUBSTANCES.

Substances other than thiamine have been used in attempts to improve the mental processes, amphetamine sulphate having been used by several workers. Using Cattell's equivalent A and B forms of Scale 2, Sargant and Blackburn (1936) found that 10 cases showed an increase of at least 10 points from $1\frac{1}{2}$ to $2\frac{1}{2}$ hours after the ingestion of the preparation. Of their cases, 38 were instances of anxiety, depression or hysteria, these showing an average gain of 4.63 points, and 8 were schizophrenics who showed an average gain of 2.37 points.

Molitch and Sullivan (1937) gave amphetamine to normal boys aged from 10 to 17 years and found that a higher percentage of improvement took place in those given 20 mgm. than in those given one half of this amount. The unit of measurement was the place in form based on knowledge, the Stanford achievement test being used.

Doses of 20 mgm. to most and of 10 mgm. to a few were used by Bradley and Green (1940) on 21 children, ranging from 9 to 13 years of age. The I.Q.'s of 13 of these varied from 90 to 110. No significant changes were found in these quotients, the revised Stanford Revision, Forms L and M being used. These last results are probably the correct findings, for these authors point out that improved performance is not due to increase of the I.Q. but to an improvement in the attention and energy, and to decrease of fatigue. Amphetamine improves the inclination, not the ability.

Glutamic acid has been found to activate brain substances, Weil-Malherbe reporting that 1 (+) glutamic acid is the only amino-acid known to be metabolized by slices of this tissue.

Nachmansohn and Machado (1943) isolated an enzyme from the brain which synthesized acetylcholine, but which became inactive on dialysis. Nachmansohn, John and Waelsch (1943) found that it was reactivated by the addition of 1 (+) glutamic acid.

Zimmerman and Ross (1944) found that, using white rats, the number of

trials for learning a maze were less than half in the rats fed upon this acid than amongst the controls. Time and accuracy scores were also significantly greater.

"A universally increased mental and physical alertness" was observed by Price, Waelsch and Putnam (1943) during the treatment of epileptics with *dl*-glutamic acid hydrochloride, but these authors were unable to correlate the incidence of seizures with the degree of improvement in mental efficiency.

A study of the effect of 1 (+) glutamic acid on the mental functioning of 69 subjects, from 16 months to 17½ years in age, has been made by Zimmerman, Burgomeister and Putnam (1946). The I.Q.'s varied from 30 to 131 before treatment, the revised Stanford Revision, Form L, the Wechsler-Bellevue, the Kuhlman-Binet, the Merrill-Palmer and the Arthur point scale being used before and after treatment. In addition, 48 cases were given the Rorschach test. Of the 69 cases, 28 suffered from convulsions, 11 of these being mentally retarded. A total of 44 mentally retarded cases was used.

The glutamic acid was given for six months, the dose being gradually raised until increased motor activity was present, or until distractability and non-co-operation occurred. The dose was then slightly reduced. Its range was from 6 to 24 gm. daily, the majority of patients being given from 12 to 24 gm. divided into three doses. The average increase of mental age after the administration of the 1 (+) glutamic acid for 6 months on the Stanford-Binet test was one year and one month and for performance tests was one year exactly. These increases represent double the increase expected in normal individuals over a 6-month period. The average I.Q.'s rose by 6.31 in the first type of test and by 7.00 in the second. Of the 516 changes in retest it ms of the Stanford-Binet tests, 90 per cent. were additions, only 10 per cent. being failures at tests passed before the administration of the glutamic acid.

The Rorschach results also showed a gain. Consistent improvement in form level, a marked reduction in inaccuracies of description and a greater facility for observing details were noted. Popular responses increased by 6 per cent. These results suggest that better social and emotional adjustment is produced by glutamic acid. This is confirmed by the clinical descriptions given by the authors.

Consideration of the permanence of the effects of glutamic acid is not dealt with, but from the description of Case 1, in whom the dose of the acid was temporarily reduced, and of Case 8 in the preliminary report of Zimmerman, Burgomeister and Putnam (1946), it is clear that when the acid is discontinued the mental state returns to its former level, a definite deterioration in behaviour and interest being noted over a period of one month in each case.

A further report, after one year's treatment, showed that the degree of improvement and the proportion of cases improving were less in the second six months than in the first. For instance, in 97 per cent. of the cases, the second I.Q. was greater than the first, but in only 53 per cent. was the third greater than the second. With regard to mental age, an average gain of 8.67 points took place during the first six months, but only 2.20 points during the second. The authors (1948) consider that a ceiling effect occurs with glutamic acid.

Use of Thiamine on Normal Children.

The reduction of improved mental functioning does not appear to occur in all tests when thiamine is used in place of 1 (+) glutamic acid. As already mentioned, the use of thiamine has been extensively investigated by Harrell, who used 110 normal individuals aged 4–20 years, most of them being from 9–19 years of age. The subjects were kept under standard conditions in an orphans' home, both the controls and those receiving the 2 mgm. additional thiamine being given indistinguishable tablets. Examination of the standard dietary was made, the thiamine intake being estimated on two days at 0.9 and 1.0 mgm. daily per case. These quantities are less than the quantity of Vitamin B₁ recommended by the Food and Nutrition Board of the National Research Council, U.S.A., in 1945, the quantities advised being 1.2 mgm. for children of from 10 to 12 years of age, and up to a maximum of 2 mgm. daily for adults, the latter quantity being less in inactive individuals.

Harrell conducted a preliminary six weeks' trial with thiamine, 18 tests being performed nine times each before the administration of the preparation. During the period of six weeks the 18 test tasks were practiced eight times each. The subjects receiving the thiamine surpassed the control group in average gain in every task, the total increase averaging 27 per cent. for the combined 18 tasks, the various increases being from 7 to 87 per cent. The nature of the tasks is exemplified by the following: Underlining, code learning, reading, division, addition, multiplication, subtraction, arithmetical problems, number span, throwing ten darts, completion of geometric designs, hand-grip, throwing ten baseballs into a pocket. Although, statistically, the assumption could be made that the superiorities could have been due to chance, all changes were on the positive side for the thiamine-fed group.

The second experiment lasted for one year and again, in various tests, the subjects receiving the thiamine showed a superiority over the controls. The nature of the tests is exemplified by the following list: Visual acuity, height, weight, remembering word pairs, code substitution, memorizing, remembering morse code, intelligence tests, reading, vocabulary, reaction-time, educational achievement. With the controls' increases 100 units, the test subjects gave rises from 113 units (weight) to 3,200 units (visual acuity—Snellen). Reading showed an increase to 2,800 units and memorizing to 533 units. Height and reaction time increased little, height to 120 units, and reaction time to 118 units.

During a second year, one quarter of the subjects who had received thiamine during the first year received the placebo and one quarter of those who had received the placebo received thiamine. The vitamin subjects gained an average of 15 per cent. in performance in the first year as against 10 per cent. in the control group, whilst, in the second year, the figures were 22 per cent. and 15 per cent. respectively.

During a third year, pairs of individuals were again reversed without their knowledge, so that those thiamine-fed received a placebo, and those placebo-fed received thiamine. The unreversed thiamine-fed cases continued to show superiority in all 11 tests, but the reversed ones, although not receiving thiamine, showed no adverse effects of the withdrawal in intelligence tests, educational

achievement, reaction time, weight or height. The improvement in these measurements continued after the cessation of the thiamine.

USE OF THIAMINE ON MENTAL DEFECTIVES.

In view of the persistence of improvement in intelligence tests after the cessation of the administration in normal children, an investigation of the effect of the vitamin upon mental defectives has been undertaken.

(1) *Selection of Cases and Dosage.*

The entire population, numbering 687 persons of all grades, of all ages and of both sexes, of a mental deficiency colony was examined. All cases who had shown no improvement in behaviour, either in their lodges, at school or at work, were given 3 mgm. thiamine once daily. This dose was 1 mgm. greater than that used by Harrell in order to ensure that the total quantity of thiamine ingested daily was at least equal to that given by this worker. In addition, the possibility existed that mental defectives might require a greater quantity than would average individuals in order to show an equal improvement.

Mental deficiency is a social concept, behaviour being of paramount importance in consideration of fitness for normal life. In this investigation three social aspects have been noted, the general behaviour in the lodges, the progress at school or work, and the social age as measured by Doll's social maturity test. In addition, the I.Q. was compared before and after treatment, the same test being used on each occasion in the same case. For cases with chronological ages of more than 14 years and with I.Q.'s of 50 or more, the Wechsler-Bellevue (verbal) test was used. The Merrill-Palmer test and the Stanford Revision of the Binet test were used on the remainder.

At the colony at which this investigation was undertaken, the nurse in charge of each lodge writes a routine yearly report upon each case. These reports were used to determine that the defectives were not improving. No case was given thiamine if any doubt existed, however slight, that any improvement had taken place during the twelve months preceding the commencement of the thiamine. The cases had been admitted to the colony from 3 to 17 years before the beginning of the investigation, so that the maximum improvement due to discipline, habit training and colony régime had already taken place. No defective was included in the series if the S.A., obtained on two occasions at six-monthly intervals over a period of one year, showed a rise, however slight.

The total number of defectives who had shown no improvement and who subsequently received the thiamine in doses of 3 mgm. once daily for a period of from 5 to 6 months, was 90, 55 being males and 35 being females. The dose used appears to be the maximum advisable, as even with this relatively low dose, the necessity arose in three cases to terminate the treatment within three months owing to increased excitability. In one man, destructiveness increased, in another noisiness increased, whilst the third became more violent-tempered. In addition, one female and one male became over-excitabile and hot-tempered, but insufficiently so to necessitate cessation of the thiamine.

At the commencement of the treatment the males varied from $6\frac{1}{2}$ years to $50\frac{9}{12}$ years and the females from $4\frac{1}{2}$ years to $52\frac{5}{12}$ years in age, the distribution being shown in Table I.

TABLE I.—*Chronological Ages of Cases before Thiamine.*

Years.	M.	F.
0	7	7
10	25	10
20	11	5
30	9	8
40	2	4
50	1	1
	—	—
Total	55	35
	—	—

Idiots, imbeciles and feeble-minded were included in each sex, the intelligence quotient ranging from 0 to 88 in the males, and from 0 to 90 in the females (Table V).

(2) *Results.*

The results may be described in four groups :

- (a) Behaviour in lodges.
- (b) Work or school reports.
- (c) Social age.
- (d) Intelligence quotients.

(a) Of the 90 cases, 12 showed improvement, 5 of these being termed slight. The stationary cases numbered 73, and 5 deteriorated in behaviour. These figures exclude the 3 cases already mentioned whose behaviour deteriorated to such a degree that the thiamine was stopped before the termination of the experimental period of from 5 to 6 months.

(b) Of 65 cases who attended school or work, 10 showed improvement, 5 of these being reported as showing a slight change only. Those remaining stationary numbered 52 and 3 deteriorated at their school or work. The remainder were too low-grade to attend either school or work.

(c) The results of testing and retesting are not precisely constant. Consequently a comparison of the S.A. immediately before the commencement of the thiamine with that after its ingestion for 5 or 6 months may not be accurate. The S.A. of the cases in this investigation were estimated at least twice, at six-monthly intervals, preceding the beginning of the administration of the thiamine. Although the S.A. after the cessation of the thiamine was frequently greater than that estimated immediately previous to the commencement of the preparation, if it was not higher than each of the preceding S.A.'s, it could not be termed a true increase. True increases have, therefore, been taken to be S.A.'s greater after the cessation of the thiamine than any of those before its commencement. True increases numbered 21 in a total of 90 cases,

and varied from 0.2 to 2.3 years. Of 18 defectives showing a decrease of S.A. after the administration of the thiamine, 10 showed a decrease before the commencement of the preparation and this decrease continued during its administration. Of 37 cases who showed the same S.A. in the two estimates preceding the thiamine, 7 showed a decrease after the administration of the preparation. Cases numbering 14 remained stationary in the two estimates before the thiamine and in that after. Of the 37 cases stationary preceding the thiamine, 16 increased, and 14 remained stationary in S.A.

TABLE II.—*Number of Cases at each S.A. before and after Thiamine.*

S.A.	Before.				After.		
	M.	F.	Total.		M.	F.	Total.
0	14	8	22	.	13	9	22
1	13	7	20	.	13	6	19
2	4	2	6	.	4	1	5
3	5	0	5	.	4	1	5
4	5	3	8	.	6	1	7
5	3	2	5	.	3	4	7
6	3	6	9	.	2	4	6
7	2	3	5	.	1	6	7
8	3	2	5	.	7	1	8
9	2	2	4	.	0	2	2
10	1	0	1	.	1	0	1
11	0	0	0	.	1	0	1
	—	—	—		—	—	—
	55	35	90	.	55	35	90
	—	—	—		—	—	—

TABLE III.—*Number of Cases Showing Changes in S.A. after Thiamine.*

	Raised.	Stationary.	Decreased.	Total.
Female	13	11	11	35
Male	23	25	7	55
	—	—	—	—
	36	36	18	90
	—	—	—	—

TABLE IV.—*Number of Cases Showing Changes after Thiamine in S.A.'s Stationary Previously.*

	Raised.	Stationary.	Decreased.	Total.
Female	4	3	2	9
Male	12	11	5	28
	—	—	—	—
	16	14	7	37
	—	—	—	—

(d) Variation in I.Q.'s after thiamine is shown in Tables V and VI. In the latter the two sexes are combined. In this table the cases who were too

low-grade to score any points on the Merrill-Palmer scale are omitted. The number of units of increase varied from 1 to 20.

TABLE V.—*Number of Cases at each Intelligence Quotient before and after Thiamine.*

I.Q.	Before.			After.		
	M.	F.	Total.	M.	F.	Total.
0	18	12	30	20	12	32
1	2	0	2	3	1	4
20	5	2	7	6	4	10
30	4	9	13	4	5	9
40	8	6	14	5	7	12
50	5	4	9	6	2	8
60	5	0	5	5	2	7
70	2	0	2	2	0	2
80	4	0	4	1	1	2
90	0	1	1	0	0	0
100	0	0	0	1	0	1
Totals	53*	34†	87	53	34	87

* No I.Q. in two cases. † No I.Q. in one case.

TABLE VI.—*Variation in I.Q.*

Test.	Raised.	Stationary.	Fell.*	Total.
Merrill-Palmer	3	3	10	16
Stanford Revision	6	3	16	25
Wechsler (Verbal)	8	5	3	16

* Inclusive of falls due to normal average yearly decrease.

DISCUSSION.

(a) *General remarks.*—The individuals who showed improvement in one form or another are shown in Table VII.

TABLE VII.—*Cases who Showed Improvement after Thiamine.*

Case No.	Improved in.				Before treatment.	
	Lodge.	Work.	S.A.	I.Q.	Ch. age.	S.A.
8	+	0	—	—	7	0.4
10	+	0	—	—	7	0.6
12	+	0	—	—	11	0.2
16	+	0	—	—	5	0.4
20	+	0	—	—	8	0.9
25	—	—	+	—	12	1.3

TABLE VII—*continued.*

Case No.	Improved in.				Before treatment.	
	Lodge.	Work.	S.A.	I.Q.	Ch. age.	S.A.
27	—	—	+	—	11	1·3
28	—	0	+	—	12	1·3
29	—	0	+	—	12	0·94
33	—	—	+	—	9	3·6
35	—	+	—	—	13	8·6
36	—	+	+	—	7	3·0
39	—	+	—	—	11	5·1
40	—	—	+	—	17	4·0
41	—	—	+	—	31	3·5
42	+	+	+	—	25	1·9
44	—	—	—	+	22	5·8
45	—	—	+	—	33	2·6
46	—	—	+	—	26	4·2
47	—	—	—	+	30	4·5
48	+	+	—	—	26	7·2
49	—	—	+	—	17	6·8
50	—	—	+	+	35	10·8
51	+	+	—	0	47	3·0
52	—	—	+	+	23	5·8
55	—	—	—	+	36	1·5
56	—	—	+	0	17	1·8
60	—	—	—	+	28	2·1
61	—	—	—	+	45	7·2
62	+	+	—	—	36	7·8
63	—	—	+	—	29	9·7
65	—	—	—	+	38	8·0
66	+	+	—	+	19	7·6
68	—	—	+	+	11	2·9
73	—	0	—	+	17	1·8
74	—	—	+	+	13	4·3
76	—	+	—	+	41	9·0
77	—	—	+	—	38	6·3
79	—	—	+	—	37	5·8
80	+	—	—	—	44	5·0
86	—	—	—	+	31	8·5
87	+	+	+	+	25	7·6
88	—	—	—	+	21	6·8
90	—	0	—	+	25	7·8
44	12	10	21	17	Totals	

+ = Improvement. — = No improvement. 0 = No school, work or test. Chronological ages to the nearest year.

This table shows that a few cases improved in more than one quality. Number 36 improved in work and S.A., No. 76 improved in work and I.Q., Nos. 50, 52, 68 and 74 improved in S.A. and in I.Q., Nos. 48, 51 and 62 improved in lodge and work, No. 66 improved in lodge, work and I.Q., No. 42 in lodge, work and S.A., and No. 87 in lodge, work, S.A. and I.Q.

The degree of improvement was seldom great, but as the cases had been in the Colony for periods varying from 3 to 17 years and had shown no improvement for a minimum period of one year before the commencement of the thiamine, any improvement, even if slight, is of interest. A slight improvement every six months will, if continued over a few years, become a considerable alteration.

Details of the improvements in lodges and at work are as follows :

Cases 8, 10, 12 and 16 take more interest in their general surroundings and Case 20, in addition, a greater interest in other children.

Case 35 has improved in reading, Case 36 in talking, and also he takes a greater interest in Montessori apparatus. Case 39 has improved in both reading and arithmetic.

Case 42 shows a general improvement in behaviour. He is more contented and less noisy. He takes a greater interest in his surroundings and talks more. He has improved slightly at work.

Case 48 is also more contented, less boisterous, and his hot tempers are becoming fewer. A general improvement has taken place in his behaviour. A slight improvement at work has been noted.

Case 51 is brighter and more alert. He is more friendly with other patients, now works at domestic occupations without being prompted, and shows no violent outbursts.

Case 62 is more cheerful and brighter. He mixes more with others in conversation and games and is more active. Whereas, previously, he was lazy, he now works hard and well.

Case 66 is now alert, active and more able to grasp instructions. He was unable to read or write, but is now eager to learn and copies written matter on bags or boxes in the general stores where he works more efficiently.

Case 76 is working more satisfactorily and is more willing to help, whilst Cases 80 and 87 are more stable in their general behaviour, the second having also improved in her work.

(b) *Chronological age.*—Those who improved in their lodges varied from 5 to 47 years of age, those who improved at school or work from 7 to 36 years of age, those who showed rises of S.A. from 7 to 38 years of age, and those who showed rises of I.Q. from 11 to 41 years of age. It is clear that both children and adults showed improvement.

(c) *Social age.*—The pre-treatment S.A.'s of those who improved varied from 0.2 to 6.8 amongst those who improved in the lodges, from 1.9 to 8.6 amongst those who improved at school or work, from 0.94 to 10.8 in those who showed a true rise of S.A., and from 1.5 to 10.8 in those who showed a rise of I.Q. Although improvements occurred amongst all levels of S.A., they were less common amongst those with S.A. below 1.0 than amongst those above this level.

SUMMARY.

A series of 90 certified mental defectives of both sexes, all ages and all grades, were given orally 3 mgm. thiamine once daily for 5 to 6 months.

All cases had shown no improvement in their behaviour in their lodges, in their school or work, or in their social ages for at least one year prior to the commencement of the administration of the thiamine.

The cases were in a colony for mental defectives and had been in this colony for periods varying from 3 to 17 years.

The behaviour of 5 cases became more violent or destructive. In 3 of these cases the necessity arose to stop the treatment after 3 months had passed. These 3 are excluded from this discussion.

Of the 90 cases who received the full course, 44 showed improvement in one or more of the following: (a) Behaviour in lodge, (b) work or school, (c) social age, (d) intelligence quotient.

Further observation of these improvements is required in order to determine whether they are permanent, and, perhaps, progressive in nature.

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