# AMERICAN JOURNAL of MENTAL DEFICIENCY

Teles Q. Brain

APRIL, 1951

VOLUME 55

NUMBER 4

A Journal devoted to the training, care, and welfare of those who, because of mental deject existing from birth or from an early age, are incapable of profiting from ordinary schooling and/or incapable of managing themselves and their affairs with ordinary prudence.

# PUBLISHED QUARTERLY BY THE AMERICAN ASSOCIATION ON MENTAL DEFICIENCY

Publication Office: 372-374 Broadway, Albany, N. Y. Editorial Office: 224 East 28th Street, New York 16, N. Y. Business Office: P. O. Box 96, Willimantic, Connecticut

7 00 PER VOLUME

414

418

\$2.00 PER COPT

Entered as second class matter September, 1940, at the Post Office at Albany, N. Y., under the Act of August 24, 1912.

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### GLUTAMIC ACID AND MENTAL DEFICIENCY A REVIEW \*

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#### PREFACE

THE rationale of any experiment is usually the result of a conglommeration of previous experiments. These experiments, taken separately, only add what seems to be discrete, abstract bits of information to man's knowledge of the human organism. However, the accumulation of these apparently discrete, abstract bits of knowledge in a seemingly evolutionary process, throw considerable light on the complex, intrinsic functions of the organism.

Prolific scientific minds are stimulated by these old experiments and they formulate new ones for which the old serve as a rationale for pursuing this or that course of investigation.

The glutamic acid experiments on mentally deficient patients evolved in such a way. This paper deals with such an evolution of experiments-one giving rise to another.

The rationale of the glutamic acid experiments with mentally deficient children, evolved from the research of others in allied fields of endeavor. Such men as Thunberg,1 Needham,2 Quastel-Wheatly,3 and Krebs,4 experimenting independently with animal

nerve, muscle, and brain, demonstrated that glutamic acid increased the activity of brain respiration, and was oxidized by peripheral nerve, and by muscle. It was concluded that "glutamic acid differed from the other amino acids by virtue of being oxidized in organs whose metabolism was mainly concerned with carbohydrates, and which are inert toward most of the other amino acids. This suggested a connection between glutamic acid and carbohydrate metabolism." 5

Weil-Malherbe,6 stimulated by the forementioned research with glutamic acid, attempted to ascertain if (1) brain could oxidize glutamic acid, and (2) the intrinsic processes involved in this oxidation, and (3) if other amino acids could be oxidized by brain. From their experiments, they concluded.

7 "The only amino acid oxidized by brain is glutamic acid which is oxidized to ketoglutoric acid and ammonia and further to water and carbon dioxide. The enzyme responsible for the oxidation of glutamic acid to ketoglutoric acid and ammonia does not attack glutamic acid so long as it is bound in the cell or to some constituents of the cell, probably a lipoid. In solution, however, the specificity is changed and glutamic acid alone is oxidized."

Nachmansohn 8 et al., concerned with

<sup>\*</sup> Paper submitted in course, "Psychology of Subnormal Children," New York University, Fall,

<sup>1</sup> Hans Weil-Malherbe. "Studies of Brain Metabolism: Mechanism of Glutamic Acid in The Biochemical Il., Vol. 30, 1936, p. 665.

<sup>2</sup> Loc. cit.

<sup>3</sup> Loc. cit.

<sup>4</sup> Loc. cit.

<sup>5</sup> Loc. cit.

<sup>6</sup> Loc. cit. 7 Ibid., p. 675.

<sup>8 &</sup>quot;Action Potential and Enzyme Activity in the Electric Organ of Electrophorus Electricus, II Phosphocreatine as Energy Source of the Action Potential," Jl. of Neurophysio., Vol. 6, 1943. pp. 383-396.

the investigation of action potential of nerves and enzyme activity, discovered that the release of acetylcholine is intrinsically connected with the potential of the nerve action.

9 (". . .) if the release of acetylcholine and its subsequent breakdown is responsible for the alterations of the nerve membrane during the transmission of the nerve impulse, chemical reactions must supply the energy for the resynthesis of acetylcholine."

It was ascertained by Nachmansohn 10 and his associates, that acetylcholine was resynthesized by the free energy of phosphocreatine, with adenosinetriphosphate acting in an intermediary capacity in the reaction. The "Acetylcholine Cycle" 11 was discerned in this investigation, and as a result of these findings, Nachmansohn 12 et al., "isolated a new enzyme, choline acetylase in a subsequent experiment. This enzyme, choline acetylase, synthesized acetylcholine in the presence of adenosinetriphosphate under anerobic and erobic conditions."

The clinical observations of Price et al.,13 were extremely provocative to Nachmansohn and his co-workers. It stimulated the formulation of another experiment concerning acetylocholine formation. Price 14 used "glutamic acid to treat epileptic patients suffering from grand mal and petit mal attacks. After the administration of glutamic acid, the electroencephalogram was utilized to observe changes in the patients brain waves. It was discerned that the brain waves of the petit mal patients changed while those of the patients suffering from grand mal were unaffected. The administration of glutamic acid to the petit mal epileptics tended to control their seizures while the grand mal epileptics were unaffected." This suggested to Nachmansohn 15 that glutamic acid may have a favorable effect on the rate of acetylcholine formation in the brain. His previous experiments had suggested an intrinsic relationship of acetylcholine in the electrical potential of nerve tissue to transmit impulses.

Nachmansohn 16 reasoned "the slow waves which appear in the electroencephalogram during attacks of petit mal may in some way be connected with a lowered rate of acetylcholine formation." Testing this hypothesis in a new experiment,17 it was ascertained that glutamic acid increased the synthesis of acetylcholine. It was further noted that when dialysis inactivated acetylcholine, the addition of glutamic acid resynthesized acetylcholine. Since glutamic acid was the only amino acid metabolized by brain, this suggested that acetylcholine may be playing a vital part in brain metabolism.

Working independently, Welshs' 18 investigation seemed to stress again the vital part that acetylcholine may be playing in brain metabolism. Welsch investigated the effect of anoxia and hypoglycemia on the production of

<sup>&</sup>lt;sup>9</sup> Ibid., p. 383. 10 Ibid., p. 390.

<sup>11</sup> Ibid., p. 391.

<sup>12 &</sup>quot;The Formation of Acetylcholine: A New Enzyme, 'Choline Acetylase,' " Jl. of Neurophysio., Vol. 6, 1943, p. 399.

<sup>13</sup> Nachmansohn et al. "The Effect of Glu-tamic Acid on the Formation of Acetylcholine,"

Jl. of Biological Chem., Vol. 150, 1943, p. 485.

14 Nachmansohn et al. "The Effect of Glutamic Acid on the Formation of Acetycholine," 11. of Biological Chem., Vol. 150, 1943, p. 485.

<sup>15</sup> Loc. cit.

<sup>16</sup> Loc. cit. 17 Ibid., p. 486.

<sup>18 &</sup>quot;Acetylcholine Level of Rat Cerebral Cortex under Conditions of Anoxia and Hypoglycemia, Il. of Neurophysio, Vol. 6, 1943, pp. 329-336.

acetylcholine in the brain of rats. From the results of his experiments, he concluded:

(probably acting through anoxia) and insulin hypoglycemia produce a decrease in the level of acetylcholine in the cerebral cortex of the rat. Therefore, it may be concluded with reasonable certainty that glucose and oxygen are important in the vivo synthesis of acetylcholine as well as in vitro synthesis as had been demonstrated by earlier investigators." The importance of Welsch's experiment is apparent because of the relation of low oxygen and low blood sugar on electrical activity in the cortex, and the production of acetylcholine.

The knowledge accummulated from the forementioned experiments, although incomplete in many aspects, formed the rational basis of subsequent studies with glutamic acid. By virtue of glutamic acid acting in a catalyst capacity in producing acetylcholine, which in turn, is intrinsically connected with the electrical changes during nerve activity, and the ability of this amino acid to re-activate acetylcholine inactivated by dialysis, provoked the subsequent glutamic acid studies.

Zimmerman and Ross <sup>20</sup> formulated an experiment using glutamic acid on rats in learning a maze. They attempted to ascertain whether glutamic acid and other amino acids would effect the learning ability of rats. The rats utilized in this experiment were divided into four groups. The first and second groups receiving neutralized and unneu-

tralized pyrrolidine carboxlyic acid,21 while the third group received aminoacetic acid. The fourth group was used as a control group and was only given basic food. The rats were first allowed to run the maze, and the performance of each group was recorded using the criteria of: (1) the number of trials necessary to master the maze: (2) the time required in seconds: (3) the number of errors made. By dividing the experiment into two parts and comparing the results of the groups (1) before receiving an amino acid and (2) after receiving an amino acid, the authors concluded:

(1) "The experimental group learned the maze in less time, required fewer trials and made fewer errors than the control group after receiving an amino acid." 22

(2) "A significant difference existed between the performance of rats fed neutralized and unneutralized pyrrolidine carboxylic acid in learning the maze than those fed aminoacetic acid." <sup>23</sup>

It was generally concluded that pyrrolidine carboxylic acid and 1-glutamic acid acted to enhance the learning ability of the rats.

Albert, Hoch and Waelsch <sup>24</sup> were the first to report the use of glutamic acid on humans. Stimulated by the experiment of Zimmerman and Ross, <sup>25</sup> they used glutamic acid on eight individuals suffering from mental deficiency. These

<sup>19</sup> Ibid., p. 335.

<sup>20 &</sup>quot;Effect of Glutamic Acid and Other Amino Acids in Maze Learning in the White Rat," Archives of Neurology & Psychiat., Vol. 51, 1944,

<sup>&</sup>lt;sup>21</sup>The rats refused to eat anything with glutamic acid hydrochloride in it. Pyrrolidine car-

boxlyic acid is a derivative of glutamic acid hydrochloride. 22 lbid., p. 451.

<sup>23</sup> Ibid., p. 450.

<sup>&</sup>lt;sup>24</sup> "Preliminary Report on the Effects of Glutamic Acid Administration in Mentally Retarded Subjects," *Il. of Nerv. & Mental Diseases*, Vol. 104, 1946, pp. 263-74.

<sup>&</sup>lt;sup>25</sup> "Effect of Glutamic Acid and Other Amino Acids in Maze Learning in the White Rat," Archives of Neur. & Psychiat., Vol. 51, 1944, pp. 446–51.

eight subjects ranged in chronological age from six to twenty-six years, and presented a spread from two to eight years in mental age. The authors attempted to pick only those cases with secondary mental deficiency (functional brain damage), but found that this was not possible due to diagnostic complications. The patients tested in this study were administered glutamic acid orally (8-10 gms. a day) after receiving a number of psychometric tests to determine their mental abilities. These tests were verbal and performance in nature and included some of the outstanding tests in the field of psychometry. The patients were retested after the administration of glutamic acid, and it was concluded from the results: 26

(1) "Glutamic acid facilitates mental functioning" (authors felt that the drop in I.Q. during the placebo period corroborated this conclusion).

(2) "Glutamic acid seems to improve the total personality."

This provocative and stimulating piece of research led Zimmerman et al. to formulate a new experiment using mentally deficient subjects. Zimmerman <sup>27</sup> and his co-workers used nine patients in this study, of which, seven were patients with convulsive disorders and two were mentally retarded without convulsions. "After a neurologic examination and appropriate laboratory studies, an initial psychometric test was performed on the subjects. Glutamic acid was then administered

in gradually increasing doses. The dose was increased to the point where increased motor activity was apparent. This dosage was maintained or reduced depending on the degree of motor activity evoked.28 The glutamic acid was administered orally in capsule, powder, or tablet form. psychometric tests used were the Stanford-Binet, 1937 Rev., Form L, the Wechsler-Bellevue Intelligence Scale, the Kuhlman-Binet intelligence test, Arthur point scale, Merrill-Palmer Performance Tests, and the Rorschach Ink Blot Test." 29 After the administration of the glutamic acid, the subjects were retested and the following conclusions drawn:

<sup>80</sup> "(a) There had been a definite improvement on verbal, motor, and personality tests following treatment.

"(b) There is definite mental improve-

ment from glutamic acid therapy.

"(c) Rorschach examination seems to indicate basic personality changes after glutamic acid administration."

In another experiment, Zimmerman <sup>31</sup> et al., working with mentally deficient children and adolescents, endeavored to corroborate the results of their previous research. In this study, they extended the duration of glutamic acid administration and used a larger number of subjects. Of the sixty-nine subjects used, forty-four were mentally retarded and twenty-eight of the total number had convulsive disorders. Utilizing the same procedure of giving the

<sup>26</sup> Albert et al., op. cit., p. 271.

<sup>&</sup>lt;sup>27</sup> 'Effect of Glutamic Acid on Mental Functioning in Children and Adolescents," *Archives of Neur. & Psychiat.*, Vol. 56, No. 5, 1946, pp. 489–506.

<sup>&</sup>lt;sup>28</sup> Zimmerman's method differed from Albert's, Hoch, Waelsh in this aspect.

Zimmerman, op. cit., p. 490.
 Zimmerman, op. cit., p. 501.

<sup>31 &</sup>quot;A Group Study of the Effect of Glutamic Acid upon Mental Function in Children and Adults," *Psychosomatic Medicine*, Vol. 9, No. 3, 1947, pp. 175–183.

psychometric tests prior to, and after, the administration of glutamic acid, Zimmerman 32 and his co-workers concluded again that there was a definite increase in the mental functioning of the subjects. In many cases, however, the small gains were negligible, but in other cases, I.Q. gains from seven to ten points were manifested. Zimmerman 33 further notes that definite changes seemed to occur in the personality of some of the subjects.

Continuing in his efforts to ascertain the effects of glutamic acid on mental functioning, Zimmerman 34 and his associates delved into a new study. This time they used sixty-seven subjects and extended the duration of glutamic acid therapy for one year. Of the subjects chosen for the study, some were children with convulsive disorders and some were mentally retarded without convulsive disorders. Psychometric tests were given prior to the glutamic acid therapy and six months after, and again following one year of treatment. The psychometric tests used were: the Stanford-Binet, Form L, the Arthur Point Scale, Merrill-Palmer Performance Test, and the Rorschach Ink Blot Test. The chronological age of the group ranged from five to sixteen years and in intelligence from 38-131. It was concluded from this study:

85 "(a) The intelligence quotients point

gain for the year ranges from zero to seventeen points, with the average gain being about eight points.

"(b) The greatest gains seem to take place during the first six months of glutamic acid therapy, the second six months adding very little."

In an attempt to discern the effect of glutamic acid upon the mental and physical growth of Mongols, Zimmerman 36 and his colleagues delved into another study. Thirty definite cases of Mongolism were used as the experimental group, while thirty control cases of non-Mongoloid retardation were matched with the experimental group.37 All experimental cases had an I.Q. below eighty and the control cases were selected to match the initial I.Q. level of the experimental group. Both groups were also matched as closely as possible for chronological age. Prior to the glutamic acid treatment, each patient in the experimental group (Mongoloid group) and in the control group (non-Mongoloid group was given the (1) Stanford-Binet Intelligence Test, Form L, 1937 Rev.; (2) the Merrill-Palmer Performance Test, and (3) the Rorschach Ink Blots.

"The glutamic acid was then administered in gradually increasing doses to the point where an optimum increase in motor and psychic activity was apparent. This dose was then maintained or reduced slightly, if too much activity was evoked. The effective dose for Mongols ranged between twentyfour and thirty-six grams per day and was arrived at empirically for each

<sup>82</sup> Ibid., p. 182.

<sup>&</sup>lt;sup>83</sup> *lbid.*, p. 182. <sup>84</sup> "The Ceiling Effect of Glutamic Acid upon Intelligence in Children and in Adolescents," Amer. Il. of Psychiatry, Vol. 104 (April), 1948, pp. 593-598.

<sup>35</sup> Zimmerman et al. "The Ceiling Effect of Glutamic Acid upon Intelligence in Children and in Adolescents," Amer. Il. of Psychiatry, Vol. 104, 1948, p. 598.

<sup>36 &</sup>quot;The Effect of Glutamic Acid upon the Mental and Physical Growth of Mongols," Amer. Il. of Psychiatry, Vol. 105, 1949, pp. 661-668. 87 Ibid., p. 662.

case." 38 From the results of this experiment, Zimmerman 39 and his associates concluded:

(a) There was a real improvement in the Mongoloid group.

(b) Glutamic acid facilitates mental functioning in this form of mental deficiency (average gain of 8 mo. in mental age during treatment period).

(c) Impressive changes were manifested in height and weight of the Mongoloids.

Zimmerman 40 feels that it can be generally concluded that glutamic acid influences the physical growth of Mongols and stimulates their mental functioning. He also points out the following:

41 "Benda postulates that Mongolism results from a disturbance in the pituitary gland. While our results cannot be interpreted as a confirmation of this thesis as a sole etiological factor in explaining Mongolism, nevertheless, since glutamic acid influences the physical growth of Mongols, it is reasonable to suppose that this improvement is mediated through the pituitary gland to a considerable extent,"

Quinn and Durling 42 made a recent experiment using glutamic acid therapy with a new twist. Instead of using glutamic acid alone, they used vitamins with it. "This experiment was conducted at the Wrentham State School, Wrentham, Massachusetts, with the following experimental design: Thirtyone children of different clinical types;

18 males and 13 females were divided into three groups: (1) Those receiving glutamic acid for six months and (2) those receiving glutamic acid plus vitamins for six months, and (3) those receiving glutamic acid for twelve months plus vitamins. Psychometric tests were administered before and after receiving glutamic acid therapy. These tests were: Revised Stanford-Binet Intelligence Scale, Form L, the Kuhlman-Binet, Wechsler-Bellevue Intelligence Scale, and the Stanford revision of the Binet-Simon Scale. The Merrill-Palmer Scale of Mental tests, and the Cornell-Coxe Performance Ability Tests." 43 It was concluded that "(1) children of group one in the experimental design-those treated with glutamic acid for six months, gained on the average of 3.9 I.Q. points; (2) the children of group two, who received glutamic acid plus vitamins, for six months, manifested a gain on the average of 3.3 I.Q. points on the Revised Stanford-Binet Intelligence Test, Form L; (3) in group three, there was an average gain for the first six months of treatment of 4.8 points in I.Q. manifested by the Revised Stanford-Binet Test, Form L. There was a small insignificant loss during the second six months for the group as a whole. The I.Q. gain for the full year was 4.4 points." 44 The authors concluded generally that the results of this experiment indicate the following: 45

<sup>88</sup> Zimmerman et al. "The Effect of Glutamic Acid upon the Mental and Physical Growth of Mongols," Amer. Il. of Psychiat., Vol. 105, 1949, p. 663.

<sup>39</sup> Ibid., p. 666.

<sup>40</sup> Ibid., p. 667. 41 Ibid., p. 667.

<sup>42 &</sup>quot;Twelve Months' Study of Glutamic Acid Therapy in Different Clinical Types in an Institution for the Mentally Deficient," Amer. 11. of Ment. Deficiency, Vol. 54, pp. 321-32.

<sup>43</sup> Ibid., p. 323.

<sup>44</sup> Quinn & Durling. "Twelve Months' Study of Glutamic Acid Therapy in Different Clinical Types in an Institution for the Mentally Defi-cient," Amer. Il. of Mental Deficiency, Vol. 54 1950, p. 331. 45 lbid., p. 332.

(a) Glutamic acid appears to stimulate mental and physical activity to some extent in certain mentally deficient children.

(b) Certain mentally deficient children gain in I.Q. 5-10 points, at least temporarily.

(c) Most substantial part of treatment is made during the initial six months of treatment.

Quinn and Durling <sup>46</sup> point out that their results are probably not as significant as Zimmerman's, in terms of large I.Q. gains, because they used a different technique of administering glutamic acid.

Waelsch 47 states in a paper summarizing the results obtained with glutamic acid, "It is too early to pass judgment on these experiments." He feels that the arguments that the gains in I.Q.'s were due to increased familiarity are untenable in view of the fact that the patients were tested several times prior to glutamic acid administration and none showed a significant variation in I.Q. Waelsch also states that the use of other tests in the glutamic acid experiments augments the tenuousness of the "Familiarity Argument." Waelsch 48 states that the results of the experiments of Zimmerman and others with glutamic acid warrant the conclusion that glutamic acid increases mental activity in mental defectives and in animals, and in addition decreases the incidence of seizures in some patients suffering from petit mal epilepsy. The best proof in the glutamic acid experiments, according to Waelsch,<sup>49</sup> rests in the fact that during the placebo period the patients in the glutamic acid experiments showed a loss of their previous intellectual gain. This loss was regained only when glutamic acid was administered. Waelsch <sup>50</sup> points out that in analyzing the intellectual gains from the glutamic acid therapy, one must differentiate whether, or not, the gain represents "the acquisition of new tools, i.e., increased intelligence or the better utilization of existing abilities."

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46 Ibid., p. 332.

<sup>47 &</sup>quot;A Biochemical Consideration of Mental Deficiency: The Role of Glutamic Acid," Am. Jl. of Mental Deficiency, Vol. 52, No. 4, 1948, pp.

<sup>305-313.

48 &</sup>quot;A Biochemical Consideration of Mental Deficiency: The Role of Glutamic Acid," Am. Il. of Mental Deficiency, Vol. 52, No. 4 (April), 1948, p. 308.

<sup>49</sup> Ibid., p. 309.

<sup>50</sup> Ibid., p. 311.