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A REPORT ON PHOSPHATIDYLCHOLINE THERAPY IN A DOWN SYNDROME CHILD[1]

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Summary.—Recent research has given support to the hypothesized existence of impaired cholinergic systems in young Down Syndrome individuals. In this study, a 2½-yr.-old Down Syndrome boy was given a phosphatidylcholine supplement over a 7-mo. period. Measures of the EEG indicate a normalization during the treatment period with minor reoccurrence of abnormalities during a placebo period. The child showed a definitive increase in speech and language skills as well as general motor skills which exceeded same aged Down Syndrome peers experiencing like training programs. These data, although preliminary, are part of a larger group study in progress and suggest that phosphatidylcholine therapy may be useful for improving neurophysiological and intellectual functioning of some Down Syndrome children.

Down Syndrome is the most common form of chromosomal aberration known to cause mental retardation including severe deficits in memory and learning processes (Thase, 1982). One of the most obvious aspects of Down Syndrome is the chronic delay in many developmental abilities such as walking, speech and language, various cognitive concepts, etc. (Pueshel, 1984; Rynders & Horrobin, 1975). Clinical and pathological neuroanatomical and neurophysiological studies have noted a number of distinct abnormalities including neuritic plaques, neurofibrillary tangles, and loss of presynaptic cholinergic markers in the cortex (Burger & Vogel, 1973; Ellis, *et al.*, 1974; Hooper & Vogen, 1976; Ropper & Williams, 1980; Solitaire & Lamarche, 1966). Yates, *et al.* (1980) have reported that CAT (choline acetyltransferase) and AChE (acetylcholinesterase) activities were low in cortical areas that exhibited plaques and tangles. Reduced cholinergic activity was also noted in the anterior perforated substance or the region containing the nucleus basalis Meynert (nbM), the major source of CAT and AChE in the cortex (Kelley

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& Moore, 1978; Johnson, *et al.*, 1981). Preliminary studies using Trisomy 16 rats, accepted animal model for Down Syndrome, have shown a significant arrest of cholinergic development in the brain (Ozand, *et al.*, 1984). These studies provide support for the notion that cholinergic deficits contribute to the clinical features of cognitive functioning in Down Syndrome.

The utilization of dietary choline as a muscarinic agonist for increasing cholinergic activity in the brain has been reported (Cohen & Wurtman, 1975; Eckernas, *et al.*, 1977; Jenden, 1978; Palacios & Kuhar, 1979; Speth & Yamamura, 1979; Jopes, *et al.*, 1984). The general findings of these studies support the view that with increased levels of serum choline, there are commensurate increases of brain acetylcholine levels. In support of this conclusion are studies showing that the utilization of dietary choline may improve memory and locomotor activity (Drachman, 1978; Beninger, *et al.*, 1984). While there have been a few isolated case studies in which choline or phosphatidylcholine was administered to patients suffering from memory or learning deficits such as those occurring in Alzheimer's disease (Fernstrom, 1981; Crook & Gershon, 1981; Corkin, *et al.*, 1983), there have been no studies to date reporting particular success with Down Syndrome. The prolonged administration of phosphatidylcholine does not produce cholinergic pharmacological side effects in the central and peripheral nervous system because complex negative feedback loops that generally dampen the consequences of increased acetylcholine synthesis (Ulus, *et al.*, 1977). Under normal depolarized states, the choline requirements of cholinergic neurons might be adequately supplied by circulating levels of choline (Goldberg, 1982). However, in states of preexisting pathological conditions, increased choline must be made available for optimal processing to occur (Jopes, *et al.*, 1977, 1978, 1984). This is presumably accomplished by increased neuronal storage of acetylcholine made available by increased free plasma choline.

It is important to demonstrate that the changes occur both behaviorally and neurophysiologically upon administration of dietary choline. Currently, psychometric and neuropsychological examinations are used to assess levels of cognitive functioning and to indicate trends of change in the course of development for Down Syndrome children. Less frequently, neurological examinations including conventional EEG are used in these assessments. These instruments are necessary but not sufficient in monitoring the results of any therapy program which has direct effects on brain chemistry and consequent functioning.

Recent advances in computer technology have generated a more sensitive and reliable method of assessment using computerized measures of EEG and evoked potentials (John, 1977). Power spectral analyses of the EEG for multiple scalp locations can be compared with age-dependent norms to provide

a quantitative measure of the deviation from normal. Unlike psychological tests, EEG and evoked potential measures are insensitive to repeated testing and are particularly suitable to longitudinal studies. As a noninvasive technique, measurements of regionally specific electrical events can be obtained which reflect the general intellectual abilities of an individual (Cantor, *et al.*, 1982; Thatcher, *et al.*, 1983) and have been used to demonstrate discriminability among various populations of learning handicapped children (Ahn, *et al.*, 1980; Cantor, *et al.*, 1985; Harmony, *et al.*, 1983). In the present study, the application of computerized EEG with serum choline assessments were used to monitor the effectiveness of phosphatidylcholine therapy on neurophysiological functioning and possibly on certain learning and memory processes in language development in a Down Syndrome child between the ages of 2.5 and 3.0 yr. It was hypothesized that with prolonged dietary consumption of phosphatidylcholine supplements, improved brain functioning would occur with changes in mental functioning and performance. The procedures and results reported here are quite preliminary as they are based on our first case study. A larger group study is underway concurrent with this report.

METHOD

Subject

The subject was a 2½-yr.-old boy diagnosed as a trisomy 21 Down Syndrome child. This child had been lagging in most developmental landmarks particularly in speech and language skills and general motor development. There was no history of cardiopulmonary dysfunctioning, and this child had never been on any medical/pharmacological therapeutic program prior to this study. Height and weight of this child were 50 cm and 12.8 kg, respectively, at the time of baseline assessments.

Materials and Apparatus

An electrode cap (Blom & Anneveldt, 1982) containing tin alloy electrodes corresponding to the full 19-lead montage of the 10-20 system (Jasper, 1958) was used. Transocular leads were employed for the detection of eye movement during the experimental session. All recording sites were referenced to linked ear lobe electrodes. All electrodes exhibited impedances of less than 10 Kohms. The amplifier bandwidths ranged from 1.5 to 30 Hz with the output down 3 db at these frequencies. An on-line rejection routine was used which excluded segments of EEG if the voltage in any channel exceeded a preset limit determined at the beginning of each session to be typical of the subject's resting EEG and EOG. In addition to computer rejection of artifact, all data were also visually edited.

The EEG conditions were passive conditions requiring only that the sub-

ject remain fairly still. No verbal or motor response was required. The method of EEG data collection is a standard condition used successfully in the collection of data from over 2,000 children from birth and adults (John, 1977; Kaye, John, Ahn, & Prichep, 1981). The neurometric measures themselves have been shown to be extremely reliable over repeated test sessions with children (Kaye, *et al.*, 1981).

For the treatment period described below, a phosphatidylcholine compound including proportions of phosphatidylinositol, phosphatidyletholamine, pyridoxine methionine, serine, and manganese was used (Supercholine, Cardiovascular Research, Ltd.). For the placebo period, nondigestible microcrystalline cellulose was used.

Procedure

Prior to introduction of the dietary regimen, the subject was given a thorough examination by a pediatrician and was found to be in a good state of health. The subject was placed on a multiple vitamin regimen (GTC No. 2; Bronson Pharmaceutical) for 3 wk. and then was brought to the Applied Neuroscience Research Institute where baseline anthropomorphic (height, weight, head circumference), serum choline, and EEG data were collected. For the EEG data to be collected, the subject was fitted with an electrocap (Electrocap, Dallas, TX) and sat on his mother's lap in a sound-attenuated booth. After establishing EEG artifacting levels, 1 min. of artifact-free eyes-open EEG was collected. In some test sessions, a second 1-min. sample of EEG was also obtained. The attainment of additional EEG was dependent upon the subject's tolerance for the testing. The subject was then put on a dietary regimen of 150 mg/kg of phosphatidylcholine (Supercholine; Cardiovascular Research, Calif.) per day while maintaining the multiple vitamin regimen. The choline substance was administered usually during breakfast and was mixed into the food or drink. After 3 wk. the subject returned for a computerized EEG test and another serum choline assessment. The family of the subject was asked to continue the prescribed diet for the next 7 mo., and the subject was to return to the laboratory for retests approximately every 6 wk. At the end of this 7-mo. treatment, the subject was placed on a dietary regimen of nondigestible cellulose for a period of 2 mo. during which time computerized EEG tests and blood samples were collected and analyzed. Prior to the experiment and during the experiment, the subject had participated in a special early language program at Loyola College in Baltimore for Down Syndrome children under age 5. All training and evaluation staff were blind to the subject's participation in this study.

Electroencephalographic Measures

A montage including 17 channels of the international 10/20 system

referenced to linked ears (O1, O2, P3, P4, T5, T6, T3, T4, C3, C4, F3, F4, F7, F8, Pz, Cz and Fz) was used. For purposes of simplifying regional descriptions, bipolar derivations were created which included the following pairwise differences: O1/P3, O2/P4, T3/T5, T4/T6, C3/Cz, C4/Cz, F7/T3, F8/T4. The following EEG measures were computed: relative power, EEG ratios, total power, percent coherence, and amplitude asymmetry (John, *et al.*, 1977). Relative power refers to the percent delta, theta, alpha, and beta frequencies noted at each derivation. The EEG ratios include a general measure of slow wave activity (delta plus theta or [dt]), a ratio of theta to alpha [ta], a ratio of the slow (delta plus theta) to fast (alpha plus beta) activity [low/high] and the total power (mean absolute power in microvolts squared across all four frequency bands for each region). The percent coherence measure reflects the degree of wave shape symmetry between the left and right pairs for each of the four frequency bands using four bipolar interhemispheric derivations (C3/Cz-C4/Cz, T3/T5-T4/T6, P3/O1-P4/O2, F7/T3-F8/T4). The amplitude asymmetry measure was computed from the absolute power (μV^2) for each site referenced to linked ears. These between hemisphere amplitude asymmetries were calculated by taking amplitude values of left and right homologous regions as:

$$(\text{left} - \text{right})/(\text{left} + \text{right})$$

It is well known that the frequency spectrum of the EEG changes with age. In the present study all measures were transformed to *Z*-scored values which have been previously regressed on age (John, *et al.*, 1977). Although the *Z*-score transforms are based on eyes closed EEG, we have found no significant differences between eyes open and eyes closed data in our data base for older children.

Results

EEG Analyses

All bipolar EEG data were *Z*-score normalized according to norming procedures discussed elsewhere (John, *et al.*, 1980; Thatcher & Cantor, 1984). Transitions of the *Z*-scores during baseline, treatment, and placebo periods were plotted to examine trends of change. The data for the ratio of slow wave to fast wave (Low/High) present in the left and right bipolar regions as well as the total power found in each of the bipolar regions are shown in Fig. 1.

There was a trend in which proportionally greater slow wave to fast wave was present in the baseline period. Following choline ingestion, however, slow wave to fast wave ratios normalized. Deviations from normal appeared for many measures by the 90th-day post initiation of treatment. This may be due to the fact that the subject had been inadvertently taken off the therapeutic

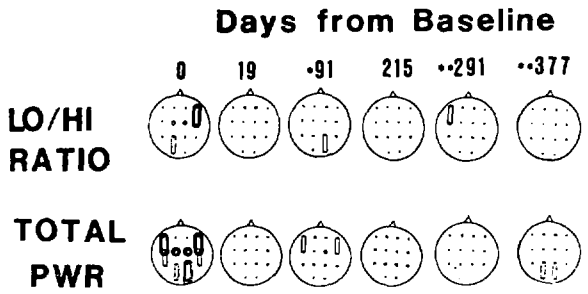

FIG. 1. *Z*-scored bipolar data of the low/high (slow wave to fast wave) ratio EEG measure and for total power (amplitude) for the time course indicated. Increasing thickness of lines encircling regions indicates increasing probability of abnormal ($p < .05$—$p < .001$). Solid lines indicate excesses, and dotted lines indicate deficits. *10-day abstinence from choline prior to test; **placebo began following test Day 215.

program for 10 days prior to this 90th-day test session. The subject was put back on the dietary regimen immediately following this test session and by Day 215 postinitiation of treatment, normalization had resumed on many of these measures. Beginning on Day 216, the subject began a substitution of placebo ingestion instead of the phosphatidylcholine complex. As noted in Fig. 1, there was little significant deviation for relative power and total power from normal across all regions during the placebo period which extended to

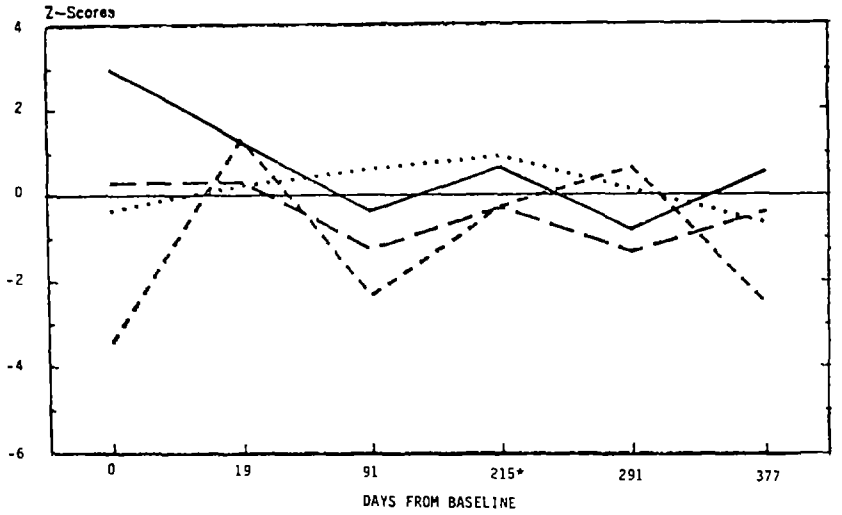

FIG. 2. *Z*-scored bipolar data of the coherence EEG measure for the time course indicated for one Down Syndrome child. A 10-day abstinence from choline occurred prior to test on Day 91. *Placebo began following Day 215. Legend: ——— central — — — temporal, - - - occipital-parietal, ... frontal-temporal leads.

162 days. Figs. 2 and 3 show plots of the EEG asymmetry measures over time. Fig. 2 shows the Z-score trends for coherence averaged across frequency for each of the bipolar regions. As noted, there is a trend toward normalization from the baseline period during the course of intervention which tends to stabilize during the placebo period. Fig. 3 shows the Z-score trends for

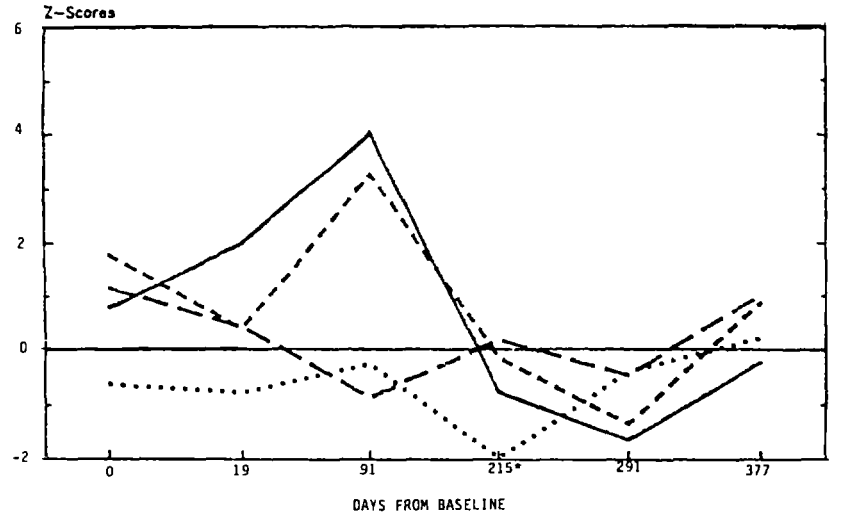

FIG. 3. Z-scored bipolar data of the amplitude asymmetry EEG measure for the time course indicated. A 10-day abstinence from choline occurred prior to test on Day 91. *Placebo began following Day 215. Legend: ——— central, — — — temporal, - - - occipital-parietal, ... frontal-temporal leads.

amplitude asymmetry measures for the bipolar regions over time. As can be seen here, amplitude asymmetry also shows normalization during the treatment period which appears to remain stable through the placebo period.

Serum Choline Analyses

Assessments were conducted on the subject during both the treatment and the placebo periods. Results from these assessments demonstrate a 2.5-fold increase in serum choline during the treatment periods relative to nontreatment periods. This increase confirms the animal model of predicted serum increase in choline following oral ingestion of a phosphatidylcholine complex.[6] It is also noteworthy that these changes in serum choline support the serum changes in rats noted by Wurtman (1983).

[6]D. S. Cantor, P. Ozand, R. W. Thatcher, & J. Rothschild, Effects of acute phosphatidylcholine ingestion on blood serum and CNS functioning. (Unpublished manuscript)

Analyses of Cognitive Performance

During the baseline period, the subject demonstrated verbal performance limited to five nouns and one preposition in his expressive language repertoire. At this time, the subject was clinically assessed as functioning at the 12-mo. level of speech and language abilities (i.e., 1.5 yr. below the norm for Down Syndrome children). Within 8 wk. from the initiation of the phosphatidylcholine dietary regimen, there was a six-fold increase in verbal output during clinical observation periods. The subject used his first two-word phrases by Week 16 following initiation of treatment. By Week 28, the subject showed ability to use two-syllable words, CVC syllables, and clean-cut sound blends. Within 32 weeks of treatment and just shy of the subject's third birthday, the subject could produce 14 consonant sounds, all vowel combinations, count to three unassisted

TABLE 1

LANGUAGE ASSESSMENT AFTER EIGHT MONTHS OF PRECURSOR THERAPY

Assessment Tool	Score
Zimmerman Pre-school Language Scale	
Auditory Comprehension	25.5 mo.
Verbal Ability	24.0 mo.
Language Age	24.7 mo.
Receptive-Expressive Emergent Language Scale	
Expressive Language	27.0 mo.
Receptive Language	36.0 mo.
Combined Language	31.5 mo.
Denver Developmental Screening Test	
Receptive Language	36.0 mo.
Expressive Language	28.0 mo.
Preschool Attainment Record	
Over-all Language Age	30.0 mo.
Early Learning Accomplishment Profile	
Completed All Items	24.0 mo.
Completed 50% of Items	30.0 mo.

and to the number 10 with assistance, capable of 105 different word productions including nouns, verbs, labels for body parts, clothing, food, household items, and animals. This child's vocabulary far exceeded the average vocabulary noted for 3-yr.-old Down Syndrome children ($M = 18.5$ words; Pueschel, 1984). At 36 wk., formal assessments were made on this subject. Table 1 shows the various assessment tools used and corresponding scores for this Down Syndrome subject (chronological age 37 mo.).

Over-all, these tests show that the subject improved from an initial lag

in all language skills of about 12 mo. to a maximum lag of 6 mo. for expressive skills only. No other Down Syndrome child in the Loyola program has shown such a significant improvement over this same length of time. With improved language and speech competencies, this subject also showed improved socialization skills and over-all motor abilities. The subject also had improved motor skills, having progressed from only being able to crawl at 26 mo. to full fledged standing, walking, and running at 36 mo. It is also interesting to note that during the placebo period, the subject continued to show progress in acquisition of skills with no significant reduction in his rate of learning. This appears to be consistent with stabilization of the EEG during that period.

Discussion

These data indicate correlated improvement in both the EEG measures and language following dietary choline ingestion. The subject was part of an initial pilot program for a larger scale study concurrent with this report. The apparent absence of a return to baseline levels during the placebo period may suggest that choline intervention need not exceed a period of 6 mo. to 1 yr. A critical feature of the intervention program may be the developmental period during which intervention provides an optimal outcome. Since functional development of the human brain undergoes a great deal of change during the first five years of life, it is hypothesized that dietary choline intervention may be most effective during this developmental period.

The reduced slow wave activity and decreased coherence have been correlated with increased intelligence of children (Ahn, *et al.*, 1983; Thatcher, *et al.*, 1983). For example, studies indicated a significant negative linear relationship with percent slow wave activity and percent coherence, respectively, with over-all Full Scale IQ. While these previous studies only indicated a correlation between certain quantitative EEG measures and intellectual performance, the findings of this preliminary study suggest a cause and effect relationship between changes in neurophysiological functioning and intellectual performance. Although preliminary and for the most part anecdotal, these data suggest a possible dietary remedial process for offsetting a lag in certain developmental processes. Dietary phosphatidylcholine or choline intervention offers the possibility for remediation for neurochemical disorders while simultaneously providing a much safer therapy than traditional drug approaches. Further research must include group studies with appropriate cross-over designs and adequate control subjects for comparisons. Such a study of this type is currently under way and the results will be reported later. This latter program also includes analyses of sensory evoked potentials which may provide more sensitive measures of neurophysiological effects since evoked potentials give an indication of cerebral activated processes related to information processing.

REFERENCES

AHN, H., BAIRD, H., PRICHEP, L., JOHN, E. R., KAYE, H., & BROWN, D. Developmental equations reflect brain dysfunctioning. *Science*, 1980, 210, 1259-1262.

BENINGER, R. J., SPENCER, A. T., & JHAMANDAS, K. Effects of chronic manipulations of dietary choline on locomotor activity, discrimination learning, and cortical acetylcholine release in aging adult Fisher 344 rats. *Neurobiol. of Aging*, 1984, 5, 29-34.

BLOM, J. L., & ANNEVELDT, M. An electrode cap tested. *EEG & clin. Neurophysiol.*, 1982, 54, 591-594.

BURGER, P. C., & VOGEL, F. S. The development of pathologic changes of Alzheimer's disease and senile dementia in patients with Down's Syndrome. *Amer. J. Pathol.*, 1973, 73, 457-476.

BZOCH, K. R., & LEAGUE, R. *Receptive Expressive Emergent Language Scale.* Tallahassee, FL: Anhinga Press, 1970.

CANTOR, D. S., THATCHER, R. W., HRYBYK, M., & KAYE, H. Computerized EEG analyses of autistic children. *J. Autism & dev. Disord.*, 1985, in press.

CANTOR, D. S., THATCHER, R. W., MCALASTER, R., LESTER, M., & HORST, R. Topographical cerebral coherence related to cognitive functioning in children. Paper presented at the Sixth Annual Southeastern Conference on Human Development, Baltimore, Maryland, 1982.

COHEN, E. L., & WURTMAN, R. J. Brain acetylcholine: increase after systemic choline administration. *Life Sci.*, 1975, 16, 1095-1102.

CORKIN, S., DAVIS, K. L., GROWDEN, J. H., USDIN, E., & WURTMAN, R. J. (Eds.) *Aging Alzheimer's disease: a report of progress in research.* New York: Raven, 1983.

CROOK, T., & GERSHON, S. (Eds.) *Strategies for the development of an effective treatment for senile dementia.* New Canaan, CT: Mark Powley Assoc., 1981.

DOLL, E. A. *Preschool Attainment Record.* Circle Pines, MN: American Guidance Service, 1966.

DRACHMAN, D. A. Central cholinergic system and memory. In M. Lipton (Ed.), *Psychopharmacology: a generation of progress.* New York: Raven Press, 1978. Pp. 651-662.

ECKERNAS, S. A., SAHLSTROM, L., & AQUILONIUS, S. M. *In vivo* turnover rate of acetylcholine in rat brain parts at elevated steady-state concentration of plasmacholine. *Acta physiol. Scand.*, 1977, 101, 903.

ELLIS, W. G., MCCULLOUGH, J. R., & CORLEY, C. L. Presenile dementia in Down's Syndrome: ultrastructural identity with Alzheimer's disease. *Neurology*, 1974, 24, 101-106.

FERNSTROM, M. H. Lecithin, choline, and cholinergic transmission. In G. A. Spiller (Ed.), *Nutrition and pharmacology.* New York: A. R. Liss, 1981. Pp. 6-24.

FRANKENBURG, W., DODDS, J., & FANDAL, A. *Denver Developmental Screening Test.* Denver, CO: LABOCA Press, 1968.

GLOVER, M. E., SANFORD, A. R., & PREMINGER, J. L. *Early Learning Accomplishment Profile for developmentally young children: birth-36 months.* Winston-Salem, NC: Kaplan Press, 1978.

GOLDBERG, A. M. The interaction of neuronal activity and choline transport on the regulation of acetylcholine synthesis. In S. Corkin (Ed.), *Alzheimer's disease: a report on progress-aging.* Vol. 19. New York: Raven Press, 1982. Pp. 327-330.

HARMONY, T. Neurometric assessment of brain dysfunction in neurological patients. *Functional neuroscience.* Vol. III. Hillsdale, NJ: Erlbaum, 1983.

HOOPER, W. M., & VOGEL, F. S. The limbic system in Alzheimer's disease: neuropathological investigation. *EEG & clin. Neurophysiol.*, 1976, 85, 1-13.

JASPER, H. H. The ten-twenty electrode system of the International Federation. *EEG & clin. Neurophysiol.*, 1958, 10, 371-375.

JENDEN, D. J. *Cholinergic mechanisms and psychopharmacology.* New York: Plenum, 1978.

JOHN, E. R. *Functional neuroscience.* Vol. II. *Neurometrics: clinical application of quantitative electrophysiology.* Hillsdale, NJ: Erlbaum, 1977.

JOHN, E R., KARMEL, B. Z., CORNING, W., EASTON, P., BROWN, D., AHN, H., JOHN, M., HARMONY, T., PRICHEP, L., TORO, A., GERSON, I., BARTLETT, F., THATCHER, R., KAYE, H., VALDES, P., SCHWARTZ, E. Neurometrics: numerical taxonomy identifies different profiles of brain functions within groups of behaviorally similar people. *Science,* 1977, 196, 1393-1410.

JOHNSON, M. V., MCKINNEY, M., & COYLE, T. Neocortical cholinergic innervation: a description of extrinsic and intrinsic components in the rat. *Exp. brain Res.,* 1981, 43, 159-172.

JOPES, R. S., JENDEN, D. J., SUBRAMANIAN, C. S., DHOPESHWARKER, G. A., & DUNCAN, J. Biochemical effects of phosphatidylcholine treatment in rats. *Biochem. Pharm.,* 1984, 33, 793-798.

KAYE, H., JOHN, E. R., AHN, H., & PRICHEP, L. Neurometric evaluation of learning disabled children. *Int. J. Neurosci.,* 1981, 13, 15-25.

KELLEY, P. H., & MOORE, K. E. Decrease of neocortical choline acetyl-transferase after lesion of the globus pallidus in the rat. *Exp. Neurol.,* 1978, 61, 479-484.

OZAND, P. T., HAWKIN:, R. L., COLLINS, R. M., REED, W. D., BAAB, P. J., & OSTER-GRANITE, M. L. Neurochemical changes in Murine Trisomy 16: delay in cholinergic and catecholaminergic systems. *J. Neurochem.,* 1984, 43, 401-408.

PALACIOS, J. M., & KUHAR, M. J. Choline: binding studies provide some evidence for a weak, direct agonist action in the brain. *Molec. Pharmacol.,* 1979, 16, 1084-1088.

PUESCHEL, S. M. *The young child with Down's Syndrome.* New York: Human Sciences Press, 1984.

RYNDERS, J., & HORROBIN, P. Project edge. In G. Friedlander (Ed.), *Exceptional infants.* Vol. 3. New York: Brunner/Mazel., 1975. Pp. 173-192.

ROPPER, A. H., & WILLIAMS, R. S. Relationship between plaques, tangles, and dementia in Down's Syndrome. *Neurol.,* 1980, 30, 639-644.

SOLITAIRE, G., & LAMARCHE, J. Alzheimer's disease and senile dementia as seen in mongoloids: neuropathological observations. *Amer. J. ment. Dis.,* 1966, 70, 840-848.

SPETH, R. C., & YAMAMURA, H. I. On the ability of choline and its analogues to interact with muscarinic cholinergic receptors in the rat brain. *Eur. J. Pharmacol.,* 1979, 58, 197-201.

THASE, M. E. Longevity and mortality in Down's Syndrome. *J. ment. defic. Res.,* 1982, 26, 177-192.

THATCHER, R. W., & CANTOR, D. S. Electrophysiological techniques in the assessment of malnutrition. In J. Brozek & B. Schurch (Eds.), *Critical assessment of key issues in research on malnutrition and behavior.* Laussane, Switzerland: Nestle Found., 1984. Pp. 116-136.

THATCHER, R. W., MCALASTER, R., LESTER, M. L., HORST, R. L., & CANTOR, D. S. Hemispheric EEG asymmetries related to cognitive function in children. In A. Perecuman (Ed.), *Cognitive Processing in the Right Hemisphere.* New York: Academic Press, 1983. Pp. 125-146.

ULUS, I. H., HIRSCH, M. J., & WURTMAN, R. J. Transsynaptic induction of adrenomedullary tyrosine hydroxylase activity by choline: evidence that choline administration increases cholinergic transmission. *Proc. Natl. Acad. Sci.,* 1977, 74, 789-800.

WURTMAN, R. J. Stimulation of catecholamine secretion by choline. *Science,* 1983, 222(Oct. 14), 188.

YATES, C. M., SIMPSON, J., MAHONEY, A., GORDON, A., & REID, A. H. Alzheimer-like cholinergic deficiency in Down's Syndrome. *Lancet,* 1980, 2, 979.

ZIMMERMAN, I. L., STEINER, Z. G., & POND, R. E. *Zimmerman Preschool Language Scale—Revised Edition.* Columbia, OH: Merrill, 1970.

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