Doubling the Rate of Neurologic Development in Down Syndrome: a Pilot Study

Patrick James Baggot, M.D.
Rocel Medina Baggot, M.D.

Introduction

After World War II, in which physical therapist Glenn Doman fought Nazi Germany as a decorated American Army commander, he and his colleagues developed methods and exercises for the neurodevelopmental rehabilitation of children. These techniques were used for children with cerebral palsy, autism, developmental delay, Down syndrome, and a wide variety of other neurodevelopmental disorders. Doman and colleagues opened the Institutes for The Achievement of Human Potential (IAHP) in 1955, and published their work in 1960 in the *Journal of the American Medical Association*.[1]

The use of educational and behavioral interventions to improve long-term neurologic outcomes is a very controversial area in developmental pediatrics. While some studies support their efficacy,[2-3] other studies failed to demonstrate benefit.[4-5] Overall, there is a paucity of data from which to draw definite conclusions. Many of the studies were performed in the remote past, and surprisingly few new data have been published since.

Recently, von Tetzchner et al.[6] published a study on the IAHP method, the first in more than three decades, in the *Journal of Developmental Neurorehabilitation*. Von Tetzchner's article contained some flaws that may have obscured a real benefit of treatment. The groups were very small (17 and 18). In each group there were many different diagnoses, including genetic syndromes, cerebral palsy (CP), epilepsy, and developmental delay, spanning a wide range of severity. These factors may have increased variance so much as to obscure a real benefit. Additionally, 13 different developmental exams were used, and only one child in the IAHP group was treated before age five. This is contrary to the IAHP method, which recommends treatment from an early age. It suggests that von Tetzchner's group did not understand the method well enough to make a valid replication. Finally, the parents felt strongly that the IAHP method was better, and this was highly statistically significant. However, this was not mentioned in the conclusion, which stated that "the substantial claims of superiority compared to other interventions made by IAHP…are not supported, but parents appear to be met in a positive manner in these programs."[6]

The current study seeks to correct the flaws of von Tetzchner's study. Instead of many and nebulous diagnoses, only one, Down syndrome, was used. Down syndrome can be verified either by physical examination or a chromosomal analysis. In von Tetzchner's study, the number of different developmental profiles used (13) is almost great as the number of subjects (17-18) in each group. In the current study, only a single developmental profile is used. All before-and-after developmental examinations were done by the professional staff of IAHP, using the developmental profile of the IAHP. The treatments were taught by IAHP staff to the parents. The number of subjects was greatly increased from 17-18 to more than 200. Variance between subjects, which can obscure conclusions, was further reduced by having each child serve as his own control.

Materials and Methods

The database consisted of a 25-year longitudinal cohort extending from 1990 to 2015, containing 248 children with Down syndrome. Of these, 24 were lost to follow-up, and eight had birth or examination dates that were unclear, making time calculations unreliable. Remaining for analysis were 216 of the 248.

Exercises

The program uses many developmental exercises, which have been detailed in books.[7-10] Important components include: movement exercise, progressing from crawling at an early age to running; passive exercises for those not able to crawl yet (patterning); early reading with flashcards; early mathematical education by counting dots on flashcards; balance and athletic activities; nutritional optimization (elimination, rotation, or other diets); and avoidance of antiepileptic drugs that hinder brain development. Functional IAHP methods to stimulate brain development are explained below.

Crawling on the floor is encouraged. A minimum of four hours daily is recommended. Developmental milestones in crawling are for the infant to elevate itself on the forearms, and then on the wrists; to lift up its head to see where it is going; and to develop convergent gaze. Close contact with the floor encourages convergent gaze development, which is necessary for reading because without it one has diplopia. Stabilizing the body develops arm strength, chest strength, and breathing strength and control, which is necessary for speech. Crawling demands significant athletic exertion from infants, evoking growth hormone, which is beneficial for brain development.

Patterning is teaching a child how a motor activity feels, or teaching the sensory portion of a motor movement. When teaching one's child to draw, one could place the pencil in the child's hands, and then move the child's hands to draw. Many parents teach their children how to ride a bike by placing the child on the seat and moving the bike passively, helping the child with balance. Most parents have done patterning.

If children have difficulty crawling, then patterning is appropriate. To teach the child to crawl by passive movement requires a team of three. The team moves the head and each limb in proper sequence. If one did not understand the purpose, patterning would appear bizarre. Crawling in a cross-pattern requires coordination of head, arms and legs. In IAHP experience, it promotes development.

Brachiation is moving across a jungle gym (ladder parallel to floor) while hanging from it by the hands. It recalls the movement of primates, before they descended from the trees to walk on the ground. It demands strength in the arms, accurate vision and hand placement, and balance. Swimming develops arm strength and breath control. Swimming stimulates brain development, especially at a young age.

Beyond crawling, children may walk, walk on uneven surfaces, climb and descend stairs, walk on logs, and run. These develop balance. Newborns are taught balance passively by swinging them through the air or moving them on a pad, replicating the movements airplanes make, such as pitch, yaw, roll, etc. Running is a strong stimulus for brain development. IAHP encourages all sports, dance, balance moves, and gymnastics. From the IAHP perspective, exercise is more about the brain than the limbs.

Many children with neurologic disabilities have small stature and small lung volumes. The children often do a treatment called "masking" for one minute per hour. Breathing from a special mask raises carbon dioxide, which is considered to stimulate lung development, chest volume, and cerebral vasodilatation. In IAHP's experience, masking may enhance chest size, stature, and head circumference.

Reading may be taught at ages 4-6 months, one word at a time. Two-inch bright red letters are printed on flashcards. This is because newborns and infants have poor ability to focus and converge. Their vision is blurry. The cerebral cortex, which interprets the images, is also under development. In this early stage, whole-word reading works best. Words are more concrete and practical, while letters are abstract. The children intuitively develop phonics while learning words. Early reading demands that the infant visual cortex develops, so as to perform at the level of an older child. Stimulating cortical development is the point.

Math is taught early by counting red dots placed randomly on a flashcard. While Arabic numerals are abstract, dots are concrete and are more easily understood by infants. This develops estimation, a right-brain form of math. Memorizing multiplication tables is an approach to math more like language—a left-brain approach. Thus, estimation develops a parallel neural circuitry for mathematics.

It is most important to make learning fun. Children naturally love learning. Parents have an urge to test the infant, but infants don't like being tested any more than adults do. Short teaching interludes (five words) with minimum testing are most effective.

Role of Staff and Caregivers

IAHP provides course work through which parents and caregivers are taught the therapy. The parents and caregivers are the therapists. IAHP staff teach the courses, counsel the therapist-parents, and perform the developmental examinations.

Developmental Assessments

The IAHP developmental profile is the Doman-Delacato profile. Each patient received a thorough developmental assessment by professional institute staff at initial examination and first follow-up. In each case a global neurologic age was determined. The chronologic ages were determined from the dates of the examination and the birth date. The ratio of global neurologic age (NA) divided by chronologic age (CA) were determined. The ratio of the global NA/CA was also determined at the first follow-up.

The median time from birth to initial exam was 16 months, and the average time was 26 months. The median time from initial exam to first follow-up was 8 months, and the average time was 13 months.

The Institutional Review Board of the IAHP approved the study.

Results

Some patients ordered materials and began some treatment, not wishing to wait for the initial assessment. In the data, one can see some children doing surprisingly well before IAHP treatment was formally begun. No Down syndrome patients were normal or better without some form of IAHP treatment. If some patients had not begun IAHP treatment before the initial assessment, the results of the study might have shown a stronger treatment effect.

Figure 1 illustrates one representative child who had a NA of 7.89 at first exam at age 12.96 months. The initial slope was 7.89/12.96=0.61. The slope of 0.61 means that the child developed at a rate of 6 months of neurologic progress per 10-month interval. At the first follow-up, the child had a NA=21.04 months at a CA=20.46 months. The slope of the second interval was (NA=21.04-7.89=13.15)/ (CA=20.46-12.96=7.5 months). The second slope (13.15/7.5=1.75) indicates that in the second interval, the child progressed at a rate of 1.75, or 17 months per 10-month interval. Thus, much more rapid developmental progress was made. For an individual patient, this figure illustrates the difference between slopes before and after IAHP treatment, which are compared in the paired T-test (see below).

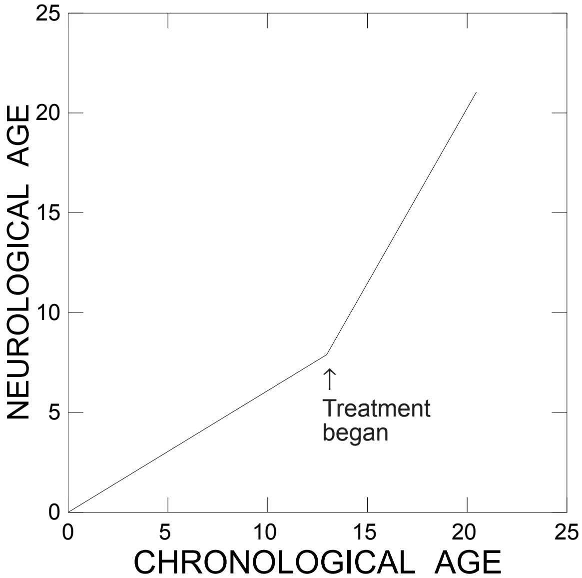

Figure 1. Rate of Neurologic Development of One Patient before and after IAHP Treatment

Figure 2 demonstrates that before treatment at IAHP, subjects had made about half as much progress as would normally be expected for their chronologic age. The figure is square, with time in months equal on X and Y axes. If neurologic progress in months were equal to chronologic time in months, it would be represented by a line from the lower left corner to the upper right corner of the diagram (slope=1.0). In Down syndrome with standard treatment (before IAHP treatment) the ratio of change (slope) in neurologic age (NA) over chronologic age (CA) had a mean of 0.55 with a mode of 0.5. These results with the developmental profile of the Institute agree with what is generally known about Down syndrome. Generally, one would expect a median intelligence quotient (IQ) of 40 with the range of 25 to 70.

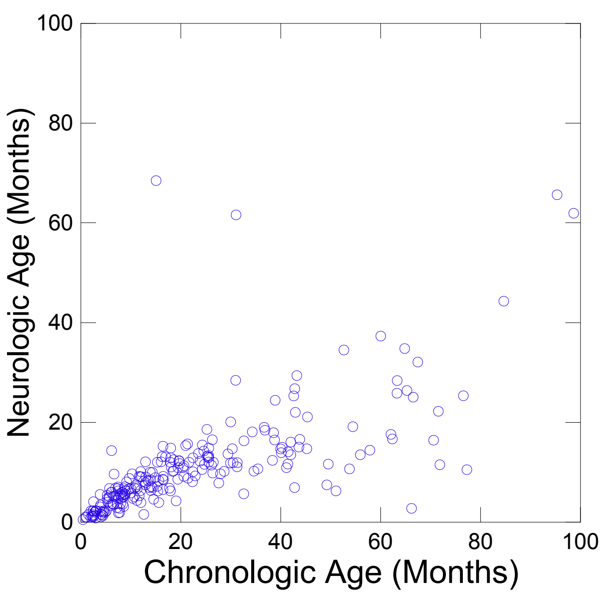

Figure 2. Neurologic Age vs. Chronologic Age at Initial Assessment

Figure 3 demonstrates that after IAHP treatment, the rate of change (slope) of neurologic progress per unit time more than doubled. The post-treatment average was 1.43, and the mode was 1.2. Note that when the first follow-up occurred at a very short interval after the initial exam, a line representing the data would have a much steeper slope. There are likely two reasons for this. One is that when stimuli are novel (learning something new rather than something old), brain development is promoted. A second reason is that if, but only if, the method did really make a difference, a short time interval accentuates the contrast between the standard method and the new method.

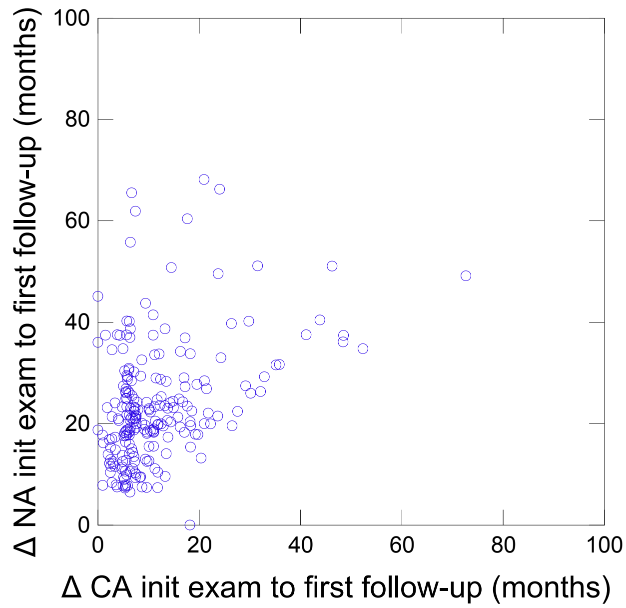

Figure 3. Change in Neurologic Age vs. Change in Chronologic Age at Follow-up Assessment

Figure 4 plots the slopes of the rate of change of NA/CA before IAHP treatment (when child was presumably receiving standard treatment) and after IAHP treatment. The frequency distribution of the rates of change is shifted to the right after IAHP treatment, towards more rapid development. A paired T-test was performed, comparing pre-treatment rate of neurologic progress in each patient with the post-treatment rate of neurologic progress in the same patient. The pre-treatment rate of neurologic development was subtracted from the post-treatment rate of neurologic development. If the pre-treatment progress was equal to the post treatment progress, this difference would be zero. If before IAHP treatment, a child made 5 months of neurologic progress in 10 months, and after treatment began made 14 months of progress in 10 months (more than doubling in the child's rate of development), the difference would be 9 months greater progress in 10 months, or 0.9.

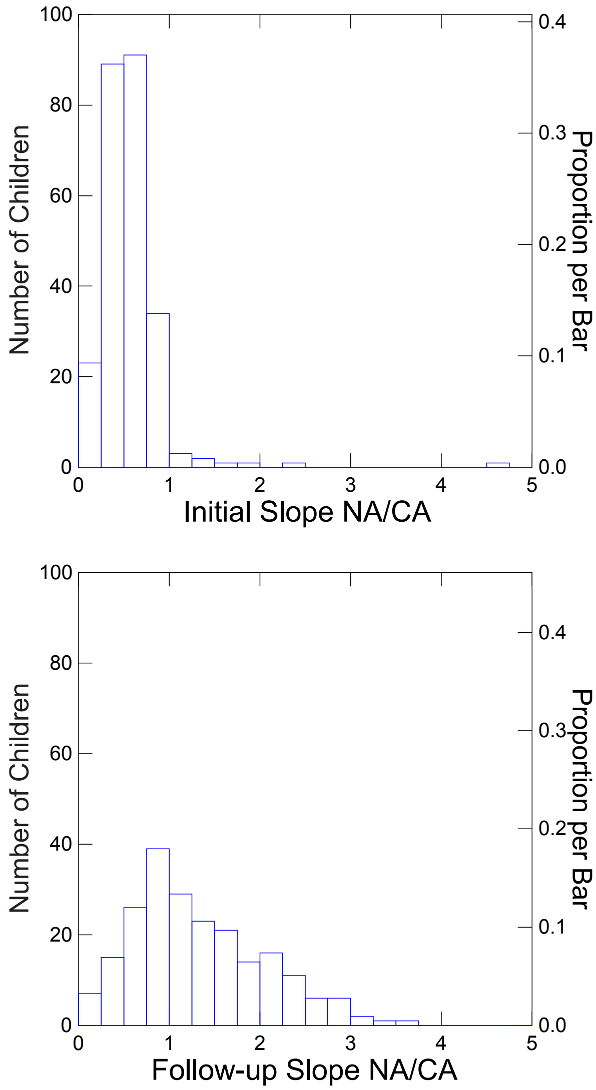

Figure 4. Rate of Change in Neurologic Age vs. Change in Chronologic Age at Initial Assessment (above) and Follow-up Assessment (below)

The mean difference was 0.87 months of neurologic progress per month. The 95% confidence interval for the difference was 0.75 to 1.0. These data indicate a strong beneficial effect of treatment. Because the confidence interval does not overlap zero, the results are statistically significant. The *P* value is $< 10^{-15}$.

Discussion

In the Middle Ages in Europe, literacy was very uncommon. Now most children in the Western world are expected to be able to read and write. The reason for the difference is that children now attend school six to eight hours per day. This previously unforeseen treatment (all children attend school) yields a previously unforeseen result (most children are now literate).

According to an old paradigm, mentally retarded children (now more often called intellectually or cognitively disabled) are uneducable and incurable. In the old paradigm, significant training would be a waste of time and effort. Many children were institutionalized. According to a newer paradigm, brain performance and intelligence are trainable. If a child has an IQ of 50, it means that in 10 months' time, only five months' progress is made. From the perspective that training improves performance, the definition of the problem also suggests the solution. This relationship makes the recommendation for intensified treatment obvious in a newer paradigm.

The effects of sensory stimulation and training on brain development have been studied in animals. Beginning in the 1960s, Rosenzweig et al.[11] spawned a large body of literature on the effects of environmental enrichment on the brain.[12] This term refers to functional methods to enhance brain development. Environmental enrichment is composed of complex inanimate and social stimulation including voluntary exercise. Sensory inputs may be auditory, visual, tactile, and/or social.[13] Beneficial effects on brain development, seen across multiple animal species including humans, include enhancement of gross and microscopic brain morphology; enhanced biochemical effects such as neurotransmitters and neurotrophic molecules; enhanced physiologic processes such as long-term potentiation; and improved behavioral and cognitive processes such as learning, memory, problem solving, and social interactions.[12] Beneficial effects on brain development can correct or improve prior neurologic insults that result from sensory deprivation. They may remediate or improve neurologic injuries, developmental delays, and/or genetic syndromes (e.g. Down syndrome).[12]

Each of the components of environmental enrichment has effects on the brain. Exercise stimulates neural plasticity. This leads to enhanced neurogenesis, learning, and cognitive performance.[14] These enhancements are seen in the cerebellum, cerebral cortex, hippocampus, and globally.[14] Exercise enhances intelligence and academic achievement both in normal children and in those with mental retardation.[15] The benefit is increased when exercise is combined mental training.[16] Combined mental and physical training can enhance neurogenesis (neuron replication) and also neuron survival (limiting apoptotic loss of newly elaborated neurons).

Different types of sensory stimulation also promote neurogenesis, brain growth, cognition, and learning. Auditory stimulation, ideally including the mother's voice, stimulates the auditory cortex so much that one can measure increased thickness of the auditory cortex with cranial ultrasound.[17] Visual sensory deprivation has profound negative effects on brain development, and visual stimulation enhances brain development.[12] Tactile stimulation also enhances brain development. Stimulation of one sensory channel (e.g. tactile) stimulates development in other sensory (e.g. visual) and motor modalities.[18] In general, there is substantial cross-pollination, such that stimulation of one sensory input or motor skill enhances other sensory channels and motor capabilities.[12] These principles work across a range of species, in normal and pathologic conditions.[12] Development is a physiologic process, and can be manipulated, just like pulse or blood pressure.

The literature on environmental enrichment provides a strong foundation in animal research for IAHP methods. Adoption literature suggests environmental enrichment also works in humans. In some institutions and orphanages, there is an "institutionalization syndrome" composed of growth delays, neuro-behavioral alterations, low IQ, disorganized attachment, and impaired language abilities.[19] These result from neglect and diminished social and sensory stimulation. Clearly, enhanced caregiving can strongly mitigate or alleviate these effects of neglect.[19]

In one study, adoption from lower socioeconomic status to higher socioeconomic status caused IQs to improve from a mean of 77 to a mean of 98.[20] Five other studies confirmed that adoption from lower socioeconomic status to higher socioeconomic status improved IQs and cognitive performance.[20] From these adoption studies, one can conclude that intelligence is not immutable, but can change. Functional stimulation (environmental enrichment) can effect a significant improvement in intelligence, development, and performance.

If a child suffered severe neglect and sensory deprivation, the child could be mentally retarded. If at age 2 he achieved one-year milestones, he would have a developmental quotient of 50 (1/2 x 100). If the child was transferred to an enriched or stimulating environment, he could make more rapid progress. During a second period, the child might make three years of progress in two years. During the second period, the child might have had a developmental quotient of 150 (3/2 x 100). This is called catch-up recovery. If at age 4 the child had four-year milestones, he would have a developmental quotient of 100 (4/4 x 100).

Some children were, in fact, severely neglected in Romanian orphanages.[21-22] One group had good results when adopted before age 2. Evaluation before adoption revealed severe global privation. Children suffered such severe neglect that they were mostly below the third percentile (mentally retarded). They had Denver developmental quotients of approximately 50. The Romanian orphan children were adopted into more loving and stimulating British families. When reexamined at age four, they had nearly complete recovery of cognitive abilities. They had intelligence quotients in the 90s (normal) after recovery. Thus, nearly complete recovery from mental retardation by means of environmental enrichment has been demonstrated in humans.[21-22] Even moderate mental retardation could have nearly complete recovery.

It was once thought that genetic, congenital, or neurologic conditions were incurable, but more recently this has been challenged.[12] In a mouse model of perinatal anoxic brain damage, environmental enrichment reversed developmental delays in inhibitory interneurons.[23] Similarly, in a rat model of cerebral palsy, environmental enrichment was able to prevent motor deficits.[24] After noise-induced impairment of the auditory cerebral cortex, environmental enrichment rescued cortical neuron function[25] and promoted recovery of degraded auditory cortical processing.[26] In rats with cerebral cortical malformations, environmental enrichment resulted in improved cognition.[27]

Studies in a mouse model of Down syndrome suggest that exercise and environmental enrichment enhance neurologic development and performance in this condition as well. In the Ts65Dn mouse, environmental enrichment led to more complex branching of the dendritic trees of neurons,[28] and exercise led to improvement in learning abilities and hippocampal neurogenesis.[29] Other studies showed that environmental enrichment improved cognitive abilities, synaptic plasticity, and visual functions,[30] and that it enhanced memory, cognition, visual system maturation, hippocampal neural plasticity, and brain function.[31]

In a human study, multi-sensory massage enhanced visual function and accelerated development in children with Down syndrome.[18] Prenatal and perinatal environmental enrichment enhanced or restored anatomy, behavior, learning, and memory in both animals[32-33] and humans.[34]

Figure 4 shows that there is more variance in patients using IAHP treatment than prior to treatment. This may be because both children and parents may make greater or lesser efforts at educational and treatment exercises. Also, in cases where follow-up was short, the novelty of a new treatment may accentuate the effect (Figure 3). When education is the treatment, teaching something new has greater effect than teaching something old. Novelty enhances the effect of environmental enrichment.

Strengths of this study may include measures to reduce variance. It is widely thought that standard therapy has no significant benefit over no therapy.[6] If similar measures were used to reduce variance, standard therapy might be shown to be superior to no therapy.

A potential weakness of this study is that all evaluations were done at IAHP. In future work, independent outside evaluation may strengthen the credibility of the conclusions. This method should also be studied with longer follow-up and across different diagnoses.

The rapid rate of improvement—more than doubling in many children—might seem hard to believe, but it is consistent with studies of adopted Romanian orphans and animal studies.

Environmental enrichment uses the concept of holistic cerebral stimulation, recognizing that to greater and lesser degrees, most areas of the brain are connected one way or another with most other areas of the brain. Depressing one cortical function tends to depress other cortical functions to some degree. Conversely, stimulating one cortical function tends to stimulate other cortical functions to some degree. This is illustrated in IAHP's experience that children, even those with profound brain injuries, can begin learning to read at age 2 or even earlier and should be given the opportunity.

Reading stimulates other cortical functions including speech. Rather than using speech as the foundation to learn visual language, one could just as easily use visual language as the foundation for speech.

Down syndrome has been thought of as primarily a chromosomal problem. The chromosomal paradigm focuses on genes triplicated by trisomy as a primary set of pathophysiologic mechanisms. Alternatively, Down syndrome could be re-imagined as a problem in developmental neurobiology. This re-imagination of Down syndrome changes the focus to different pathophysiologic mechanisms, and points toward different treatments.

Conclusion

Down syndrome children have much greater potential for development than many realize. Methods discussed here for environmental enrichment should be studied for their potential to enhance brain development in other conditions, and in normal children as well.

Patrick James ("Paddy Jim") Baggot, M.D., is an obstetrician/gynecologist and medical geneticist, practicing as an independent physician in Koreatown, Los Angeles, Calif. Contact: pjbaggot@hotmail.com. **Rocel Medina Baggot M.D.**, is an obstetrician/gynecologist.

Conflict of Interest Statement: None of the authors has any real, potential, or perceived conflict of interest to report relevant to the material of the article.

Acknowledgements: The tireless efforts of parents, caregivers and children are gratefully acknowledged. The contributions of Teruki Uemora, Janet Doman, past and present staff of IAHP and Glen Doman (deceased) are gratefully acknowledged. This research was supported by the International Foundation for Genetic Research (Michael Fund), which has now closed.

REFERENCES

1. Doman RJ, Spitz EB, Zucman E, Delacato C, Doman G. Children with severe brain injuries: neurological organization in terms of mobility. *JAMA* 1960;174:257-262. doi: 10.1001//jama.1960.03030030030037007.
2. Neman R, Roos P, McCann RM, Menolascino FJ, Heal LW. Experimental evaluation of sensorimotor patterning used with mentally retarded children. *Am J of Ment Defic* 1975;79:372-384.
3. IAHP. A summary of concepts, procedures and organization. Institutes for the Achievement of Human Potential, Philadelphia, Pa.; 1964.
4. Robbins P. Test of the Doman-Delacato rationale with retarded readers. *JAMA* 1967;202:389-393. doi: 10.1001/jama.1967.03130180055008.
5. Sparrow S, Zigler E. Evaluation of a patterning treatment for retarded children. *Pediatrics* 1978;62(2):137-150.
6. Von Tetzchner S, Verdel M, Barstad BG, et al. The effect of interventions based on the programs of The Institutes for the Achievement of Human Potential and Family Hope Center. *Dev Neurorehabil* 2013;16:217-229.
7. Doman GJ, Doman JJ. *How to Teach Your Baby to Read*. Garden City Park, N.Y.: Square One Publishers; 2006.
8. Doman GJ, Doman JJ. *How to Teach Your Baby Math*. Garden City Park, N.Y: Square One Publishers; 2006.
9. Doman GJ, Doman D, Hagy B. *How to Teach Your Baby to Be Physically Superb.* Garden City Park, N.Y.: Square One Publishers; 2005
10. Doman GJ. *What to Do about Your Brain-Injured Child.* Garden City Park, N.Y.: Square One Publishers; 2005.
11. Diamond MC, Krech D, Rosenzweig MR. The effects of an enriched environment on the histology of the rat cerebral cortex. *J Comp Neurol* 1964;123:111-120.
12. Sale A, Berardi N, Maffei L. Environment and brain plasticity: towards an endogenous pharmacotherapy. *Physiologic Reviews* 2014;94(1):189-234.
13. Rosenzweig MR, Bennett EL, Hebert M, Morimoto H. Social grouping cannot account for cerebral effects of enriched environments. *Brain Res* 1978;153:536-576.
14. Thomas AG, Dennis A, Bandettini PA, Johansen-Berg H. The effects of aerobic activity on brain structure. *Front Psychol* 2012;3(86):1-9. doi: 10.3389/fpsyg.2012.00086.
15. Tomporowski PD, Davis CL, Miller PH, Naglieri JA. Exercise and children's intelligence, cognition and academic achievement. *Educ Psychol Rev* 2008;20:111-131.
16. Curlik DM 2nd, Shors TJ. Training your brain: Do mental and physical (MAP) training enhance cognition through the process of neurogenesis in the hippocampus? *Neuropharmacology* 2013; 64(Jan):506-514.
17. Webb AR, Heller HT, Benson CB, Lahav A. Mother's voice and heartbeat sounds elicit auditory plasticity in the human brain before full gestation. *Proc Natl Acad Sci USA* 2015;112(10):3152-3157.
18. Purpura G, Tinelli F, Bargagna S, et al. Effect of early multisensory massage intervention on visual functions in infants with Down syndrome. *Early Hum Dev* 2014;90:809-813.
19. Zeanah CH, Nelson CA, Fox NA, et al. Designing research to study the effects of institutionalization on brain and behavioral development: the Bucharest early intervention project. *Dev Psychopathol* 2003;96(15):8790-8794.
20. Duyme M, Dumaret AC, Tomkiewicz S. How can we boost IQs of "dull children"?: A late adoption study. *Proc Natl Acad Sci USA* 1999;96(15):8790-8794.
21. Palacios J, Brodzinsky D. Review: Adoption research: trends, topics, outcomes. *Int J Behav Dev* 2010;34(3):270-284.
22. Rutter M. Developmental catch-up, and deficit, following adoption after severe global early privation. English and Romanian Adoptees (ERA) Study Team. *J Child Psychol Psychiatry* 1998; 39:465-476.
23. Komitiva M, Xenos D, Salmaso N, et al. Hypoxia-induced developmental delays of inhibitory interneurons are reversed by environmental enrichment in the postnatal mouse forebrain. *J Neurosci* 2013;33(33):13375-13387.
24. Marquez MR, Stigger F, Segabinazi E, et al. Beneficial effects of early environmental enrichment on motor development and spinal cord plasticity in a rat model of cerebral palsy. *Behav Brain Res* 2014;263:149-157.
25. Jiang C, Xu X, Yu L, Xu J, Zhang J. Environmental enrichment rescues the degraded auditory temporal resolution of cortical neurons induced by early noise exposure. *Eur J Neurosci* 2015;42(5):2144-2154.
26. Zhu X, Wang F, Sun X, Kilgard MP, Merzenich MM, Zhou X. Environmental acoustic enrichment promotes recovery from developmentally degraded auditory cortical processing. *J Neurosci* 2014;34(16):5406-5415.
27. Jenks KR, Lucas MM, Duffy BA, et al. Enrichment and training improve cognition in rats with cortical malformations. *PloS* One 2013;8(12):e84492. doi:10.1371/journal.pone.0084492.
28. Dierssen M, Benavides-Piccione R, Martinez-Cue C, et al. Alterations of neocortical pyramidal cell phenotype in the Ts65Dn mouse model of Down syndrome: effects of environmental enrichment. *Cereb Cortex* 2003;13:758-764.
29. Llorens-Martin MV, Rueda N, Tejeda GS, et al. Effects of voluntary physical exercise on adult hippocampal neurogenesis and behavior of Ts65Dn mice, a model of Down syndrome. *Neuroscience* 2010;171:1228-1240.
30. Begensic T, Spolidoro M, Braschi C, et al. Environmental enrichment decreases GABAergic inhibition and improves cognitive abilities, synaptic plasticity, and visual functions in a mouse model of Down syndrome. *Front Cell Neurosci* 2011;5:29.
31. Begensic T, Sansevero G, Baroncelli L, Cioni G, Sale A. Early environmental therapy rescue brain development in a mouse model of Down syndrome. *Neurobiol Dis* 2015; 82:409-419. doi: 10.1016/j.nbd.2015.07.014.
32. Kida E, Rabe A, Walus M, Albertini G, Golabek AA. Long-term running alleviates some behavioral and molecular abnormalities in Down syndrome mouse model Ts65Dn. *Exp Neurol* 2013;240:178-189.
33. Chakrabarti L, Scafidi J, Gallo V, Haydar TF. Environmental enrichment rescues postnatal neurogenesis defect in the male and female Ts65Dn mouse model of Down syndrome. *Dev Neurosci* 2011;33(5):428-441.
34. Baggot PJ, Baggot RM. Fetal therapy for Down syndrome: report of three cases and a review of the literature. *J Am Phys Surg* 2014;19:200-204.