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18. A sample of lipids (DPPC, Fluka, Buchs, Switzerland; DHPC, Sigma Chemical Company, St. Louis, Mo.), at 2 mg/ml in 0.2*M* carboxyfluorescein (Kodak, recrystallized) at *p*H 8.6, was sonicated to clarity (15 minutes) at 70 W with a Branson B-12 Sonicator. The sample was chilled, centrifuged for 10 minutes to remove any metal fragments, and the liposomes obtained were separated on a Sephadex G-50 column at *p*H 7.5. The CF at *p*H 8.6 was used for sonication in an attempt to ensure the presence of the maximum amount of PHC in the charged form. When the liposomes were run on the G-50 column, *p*H 7.5 buffer was used to bring them to a physiologic range. No CF loss was noted during the elution step. The liposome fraction obtained was kept on ice and assays were started within 1 hour after preparation. After 24 hours at 4° to 6°C, some leakage of fluorescence could be detected, but not significantly more for liposomes containing PHC than for pure DPPC or DHPC vesicles.
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Developmental Equations for the Electroencephalogram

Abstract. *Thirty-two linear regression equations predict the frequency composition of the electroencephalogram within four frequency bands, for four bilateral regions of the brain, as a function of age. Equations based on such data from large groups of healthy children in the United States and Sweden are closely similar. These equations describe the development of the electrical activity of the normal human brain, independent of cultural, ethnic, socioeconomic, or sex factors.*

The frequency composition of the electroencephalogram, or EEG, reflects the age and the functional status of the brain. With maturation the dominant frequency becomes more rapid, and brain damage, dysfunction, or deterioration causes frequency slowing in the brain regions involved (*1*). These conclusions were initially based on qualitative impressions gained by visual examination of ink tracings. By means of analog filters and special-purpose frequency analyzers and, more recently, by using general-purpose digital computers implementing the fast Fourier transform (FFT), these conclusions have been confirmed by quantitative studies of changes in the EEG frequency spectrum with age and with brain disease (*2*).

The EEG frequency spectrum is considered to contain four major frequency bands: delta (1.5 to 3.5 Hz), theta (3.5 to

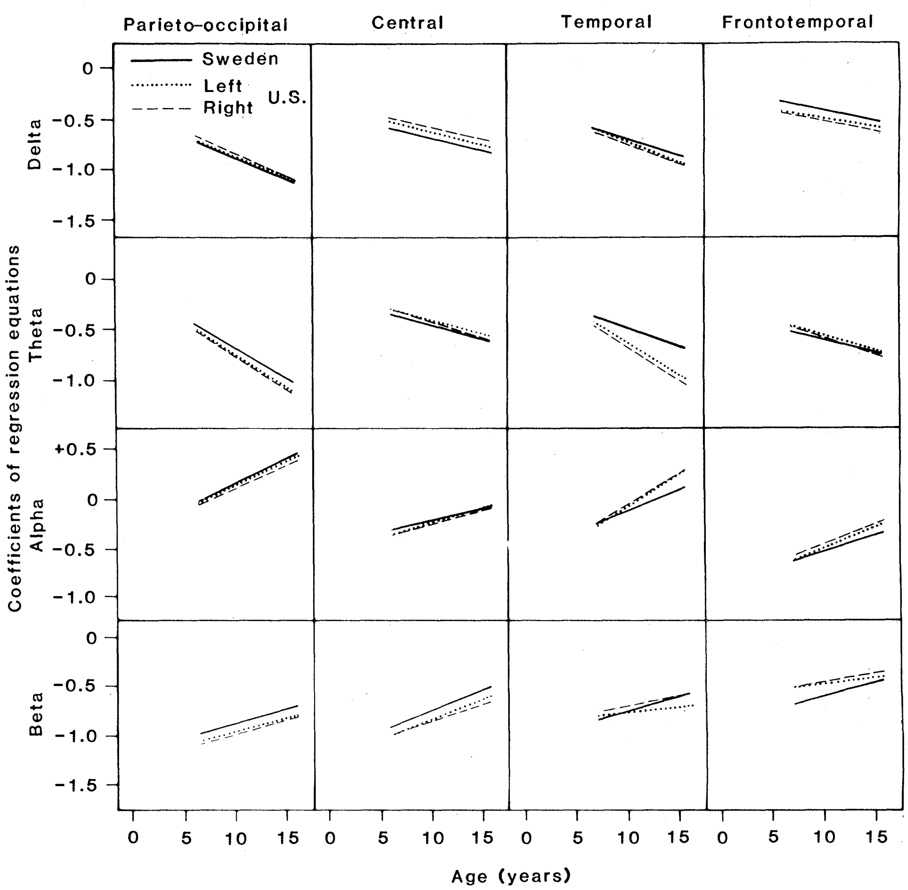

Fig. 1. Regression equations for data from U.S. children (N = 306) and Swedish children (N = 342) for each frequency band and derivation. Dashed lines (from right side of head) and dotted lines (left side) describe the equations derived from U.S. children. Solid lines describe the Swedish data. The data are valid for children aged 6 to 16 years.

7.5 Hz), alpha (7.5 to 12.5 Hz), and beta (12.5 to 25 Hz) (*3*). Factor analysis of the EEG frequency spectrum has shown that these four bands correspond to independent factors (*4*).

Using sharply tuned analog band-pass filters, Matoušek and Petersén (*5*) obtained EEG samples, recorded during 1-minute resting (eyes closed) periods, from 561 healthy male and female Swedish children aged 1 to 21 years. After visually editing the samples to remove artifacts, and separating the samples into groups according to the years of age of the children, they computed for each age group, in yearly increments, the means and standard deviations of the EEG amplitude in the delta, theta, alpha, and beta bands in bilateral frontotemporal, temporal, central, and parieto-occipital derivations (*6*). Using these data, Matoušek and Petersén constructed normative tables that revealed smooth changes in each of these parameters as the mean age of the children in each group increased (*5*).

In our laboratories, 60 seconds of artifact-free EEG samples (recorded with eyes open and eyes closed) have been gathered routinely from approximately 750 normal and 2500 learning-disabled children aged 5 to 21 years. In our system we use computer software for the automatic on-line rejection of data contaminated by artifacts (*7, 8*). Subsequent visual editing prior to quantitative analysis removes any artifacts that elude the computer algorithm (*9, 10*). In the first 1000 sessions, these samples were obtained both at the beginning and end of a 1-hour examination of evoked potentials.

Comparisons of test-retest reliability (within session) of absolute power measures in each frequency band revealed poor replicability in both the eyes open and eyes closed condition. Therefore, these measures were transformed to relative power (percentage) by dividing the absolute power in each frequency band by the total power in all four bands, separately or each derivation. For the eyes open EEG, substantial variability remained in spite of this transformation. However, relative power measures revealed excellent replicability for the eyes closed EEG (*11*). Similar conclusions have been reached by others (*12*). This may indicate that the relative power of the eyes closed EEG is less sensitive to changes in alertness or attention than other measures studied.

The distribution of relative power values in large samples of normally functioning children was examined to develop valid statistical criteria for evaluation of individual values. A logarithmic transformation, $\log(x/100 - x)$, was found to achieve approximately Gaussian distributions for all relative power measures (x). EEG features could therefore be subjected legitimately to Z-transformations relative to the corresponding means and standard deviations of data samples obtained from groups of healthy children. Interpretation of the numerical data yielded by quantitative analysis of brain electrical activity can thereby be greatly simplified, since the probability that any given measure is abnormal can then be assessed by conventional parametric statistics. Electrophysiological evaluations in which clinically relevant features are quantitatively extracted and subjected to Z-transformation are referred to as neurometric examinations.

The orderly nature of the published normative tables as a function of age (*5*), and our findings that relative power measures were replicable and amenable to parametric evaluations, encouraged us to construct regression equations to describe maturational changes in the EEG, to test the accuracy of these equations in diverse groups of children, and to evaluate their sensitivity to brain disease or dysfunction. Our first step was to convert the published mean values and standard deviations to relative power (*8, 13*), and then to transform these data to $Y = \log(x/100 - x)$, where x refers to the relative power value. A polynomial regression equation across the population means as a function of age was computed for each transformed EEG parameter in each derivation. This takes advantage of the full body of data to minimize irregularities reflecting the grouping of children according to age of nearest birthday, small sample sizes, and possible sampling errors at each age in the published data.

The transformed data of group means were fitted with sixth order orthogonal (Chebyshev) polynomials (*14*). F tests revealed many significant contributions by terms up to the fourth order, with higher order terms contributing less than 1 percent of the variance. The equations were reduced to standard polynomials of the form: $\overline{Y} = C_0 + C_1t + C_2t^2 + C_3t^3 +$

Table 1. Coefficients of linear regression equations $C_0 + C_1t$, for relative power and standard deviations for U.S. children ($N = 306$) and Swedish children ($N = 324$), for $\log(x/100 - x)$, where x denotes relative power in each frequency band. No valid estimate of standard deviation of the relative power can be computed from the published Swedish data (*5*). The data are valid for children aged 6 to 16 years.

Derivation	Delta				Theta				Alpha				Beta			
	Relative power		Standard deviation		Relative power		Standard deviation		Relative power		Standard deviation		Relative power		Standard deviation	
	C_0	C_1	C_0	C_1	C_0	C_1	C_0	C_1	C_0	C_1	C_0	C_1	C_0	C_1	C_0	C_1
Parieto-occipital																
U.S. P_3O_1	−.41	−.043	.28	−.01	−.06	−.063	.31	−.01	−.34	.047	.41	−.02	−1.24	.029	.23	−.01
U.S. P_4O_2	−.37	−.046	.29	−.01	−.06	−.063	.31	−.01	−.37	.049	.43	−.02	−1.25	.030	.29	−.01
Sweden*	−.44	−.040			−.12	−.055			−.38	.050			−1.24	.029		
Central																
U.S. C_3C_Z	−.33	−.026	.25	−.01	−.11	−.028	.21	.00	−.52	.028	.40	−.02	−1.25	.036	.19	−.01
U.S. C_4C_Z	−.33	−.025	.20	.00	−.10	−.030	.22	−.01	−.52	.027	.34	−.01	−1.22	.035	.20	−.01
Sweden*	−.35	−.024			−.14	−.026			−.38	.023			−1.20	.042		
Temporal																
U.S. T_3T_5	−.31	−.039	.26	−.01	.00	−.060	.30	−.01	−.72	.062	.38	−.01	−.086	.008	.46	−.02
U.S. T_4T_6	−.35	−.036	.25	−.01	.01	−.061	.36	−.01	−.67	.059	.43	−.02	−0.91	.011	.38	−.02
Sweden*	−.41	−.029			−.13	−.043			−.55	.043			−1.04	.027		
Frontotemporal																
U.S. F_7T_3	−.31	−.018	.25	−.01	−.25	−.028	.31	−.01	−.89	.040	.27	−.01	−0.60	.010	.55	−.03
U.S. F_8T_4	−.31	−.019	.24	−.01	−.24	−.030	.25	−.01	−.81	.035	.28	−.01	−0.61	.012	.45	−.02
Sweden*	−.30	−.020			−.28	−.025			−.83	.032			−0.80	.029		

*These equations are based on pooled data from left and right sides, as published by Matoušek and Petersén (*5*).

C_4t^4, where t is age in years minus one (*15, 16*) and the coefficients C_i are constants. Thus, 16 equations were obtained (for delta, theta, alpha, and beta in frontotemporal, temporal, central, and parieto-occipital derivations), each with five coefficients (*17*).

If the actual value of an EEG frequency parameter measured from a child is x, if that value is transformed to $Y = \log(x/100 - x)$, if the predicted mean value $\bar{Y}$ for the corresponding EEG parameter is calculated by entering the age t of the child minus one into the appropriate polynomial, and if S is the corresponding standard deviation of the mean, then $Z = (Y - \bar{Y})/S$ defines the Z-transformation. This transformation permits estimation of the probability of obtaining the observed value Y by chance, for that EEG parameter in that anatomical derivation, in a normal healthy child of age t.

The precision with which such measurements fell within the predicted distributions was tested in an independent group of 140 normal, healthy children, all performing at grade level in school. Since the measurements were performed separately for the derivations on the left and right sides, there were 32 EEG parameters computed for each child, or 4480 values for the total group. Of these values, 4202 (93.79 percent) fell within the 5 percent confidence level from the mean, while 6.21 percent fell beyond the 5 percent confidence level (false positives). Of these false positives, 4.12 percent fell beyond the 5 percent but not the 1 percent confidence level, 1.72 percent beyond the 1 percent but not the 0.1 percent level, and 0.37 percent beyond the 0.1 percent level. This distribution is quite similar to that predicted by the equations (*11*). These false positives were distributed across the set of normal children and were not found to occur within any specific subgroup. The observed incidence of false positives in these data, when subjected to quantitative analysis, compares favorably with the 12 to 30 percent reported with subjective EEG analysis of normal children (*18*).

Further, the composition of our sample permitted us to define and compare different matched subgroups, each with no less than 25 members: white children from middle-class suburbs of New York, white children from lower income communities outside New York City, black children from the Harlem district of New York, black children from small farm communities in Barbados (*19*), male children, female children, and groups with different age composition across the age range 5 to 12 years. None of these subgroups showed an incidence of false positives at the $P < .05$ level which was significantly greater than chance, nor was any group significantly different from any other group at the $P < .05$ level with respect to the distribution of any of the 32 EEG parameters, as assessed by χ^2 tests (*11*).

While these computations were being performed, the same EEG parameters were being extracted from additional children in our normal sample. Because the total size of our normal sample in the 6- to 16-year age range ($N = 600$) was greater than the Swedish sample in that range ($N = 324$), we derived a new set of regression equations for that age range based completely on U.S. children. We examined the medical and developmental histories of this group of children. Following the stringent criteria used by Matoušek and Petersén (*5*), first we excluded from the "normal" sample all children who could plausibly be considered "at risk" because of extreme pre- or perinatal trauma, with childhood histories that included prolonged high febrile illness, loss of consciousness due to concussions, convulsions, extreme behavior problems, failure in school at any grade level, a standard score on the Wide Range Achievement Test below grade level in any skill (below 90), an IQ estimate from the Peabody Picture Vocabulary Test below 90, or any grade below passing level on school report cards for 2 years prior to our evaluation. Second, any children whose raw EEG record revealed apparent epileptiform activity on visual examination were excluded. Only 306 of our 600 ostensibly "normal" volunteers could be used after this pruning (*20*).

This confirmed normal sample was then divided into two split-half subgroups, balanced for chronological age and date of test. A regression equation was then computed for all 32 EEG parameters for the individuals in the first-half subgroup across the age range 6 to 16 years. The incidence of false positives (Z-transformation values beyond the .05 probability level) was found to be 6.7 percent. Since this value seemed acceptably close to the level expected by chance, the two groups were merged and final regression equations were computed for the 32 EEG parameters. We found that the data could be adequately fitted by a set of linear equations of the form $C_0 + C_1t$ (*21*). Since our goal was now to compare regression equations describing these EEG parameters in two independent populations, new regression equations were computed on the group means of the Swedish children (*5*) across this more restricted age range. These data were also well fitted by a linear equation. Presumably the higher order polynomial terms in our initial regression equations were due to the rapid changes of these parameters in the first 5 years and their

Table 2. Coefficients in fourth-order polynomial regression functions for logarithmic transform of relative power. The standard deviations of the log relative power for each frequency band in every derivation were as follows. Central: delta, 0.17550; theta, 0.19706; alpha, 0.27472; beta, 0.14968. Temporal: delta, 0.19515; theta, 0.21789; alpha, 0.25411; beta, 0.20643. Parieto-occipital: delta, 0.22553; theta, 0.21229; alpha, 0.26090; beta, 0.17554. Frontotemporal: delta, 0.13585; theta, 0.13763; alpha, 0.18157; beta, 0.19110. Based on data from (*5, 16*).

Frequency band	C_0*	C_1	C_2	C_3	C_4
			F_7-T_3 *and* F_8-T_4		
Delta	0.05026793	− 0.02864339	0.00268197	− 0.00024649	0.00000726
Theta	− 0.49661124	0.02704753	− 0.00219526	− 0.00012897	0.00000637
Alpha	− 1.19101954	0.11536730	− 0.01021430	0.00052462	− 0.00001035
Beta	− 0.69595569	− 0.05826711	0.00636409	− 0.00002820	− 0.00000592
			C_Z-C_3 *and* C_Z-C_4		
Delta	0.01337487	− 0.11086171	0.01164788	− 0.00062616	0.00001153
Theta	− 0.39715552	0.07269696	− 0.01230534	0.00065100	− 0.00001268
Alpha	− 0.94571376	0.17154604	− 0.01993426	0.00110665	− 0.00002212
Beta	− 0.95783710	− 0.09368554	0.01825462	− 0.00099472	0.00001902
			T_3-T_5 *and* T_4-T_6		
Delta	0.01312087	− 0.10731703	0.01305750	− 0.00081664	0.00001665
Theta	− 0.41266653	0.10212188	− 0.02114789	0.00119691	− 0.00002312
Alpha	− 1.22848630	0.18772255	− 0.01056178	0.00017109	0.00000299
Beta	− 0.70206171	− 0.10165458	0.01017377	− 0.00014639	− 0.00000520
			P_3-O_1 *and* P_4-O_2		
Delta	0.14496185	− 0.20564358	0.02497562	− 0.00150341	0.00003163
Theta	− 0.41780865	0.13641311	− 0.03206439	0.00204809	− 0.00004317
Alpha	− 1.14453661	0.25399819	− 0.02050309	0.00080608	− 0.00001157
Beta	− 1.06820560	− 0.06939101	0.01273942	− 0.00057574	0.00000711

*C_0 does not include the calibration constant, which must be determined separately for any set of methods used to extract the frequency measures.

leveling off between 17 and 21 years.

Figure 1 illustrates the two sets of regression equations derived from the U.S. and Swedish children. Table 1 presents the two coefficients of the corresponding linear equations, $C_0 + C_1t$, where C_0 is the intercept, C_1 the slope, and t the age of the child. Table 1 also gives the two coefficients of the linear regression equation for the standard deviations for each frequency band in each derivation. The data reveal a striking similarity between the two sets of regression equations. The close correspondence of these two independent descriptions of the evolution of these EEG parameters in children from two different countries suggests that the equations constitute a first approximation to a quantitative description of the rules governing the maturation of these EEG parameters in the normal healthy human brain. Since we found that the observed values are replicable within individuals and across cultures, we suggest that they may be generally applicable, independent of cultural, ethnic, socioeconomic, sex, or age factors. These new linear regression equations, based on automatic digital techniques of data acquisition and analysis, outdate the fourth-order polynomials initially derived from the Swedish data. However, pending extension of our normative data to a wider age range, the initial equations retain practical utility for evaluation of individuals in the age ranges 1 to 5 and 17 to 21 years. Accordingly, the coefficients of the equations $\overline{Y} = C_0 + C_1t + C_2t^2 + C_3t^3 + C_4t^4$, and the corresponding standard deviations, are presented in Table 2.

We have also obtained evidence (*22*) that although the incidence of improbable Z values in healthy children is seldom beyond the chance level for these stable EEG parameters, positive findings occur in a high proportion of children at risk for various neurological diseases and for brain dysfunctions related to learning disabilities.

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6. Each of the children was carefully screened to exclude a wide variety of conditions that might cause abnormal brain function. From each child's EEG, six 10-second epochs without artifacts were visually selected. EEG's from bipolar derivations, F_7T_3, F_8T_4, T_3T_5, T_4T_6, P_3O_1, P_4O_2, C_3C_z, C_4C_z, were processed with a broadband analog frequency analyzer yielding the amplitude of the EEG activity in delta, theta, alpha 1 (7.5 to 9.5 Hz), alpha 2 (9.5 to 12.5 Hz), beta 1 (12.5 to 17.5 Hz), and beta 2 (17.5 to 25 Hz). The frequency analyzer output values for each record were automatically taped, and averages and standard deviations for each age group were computed digitally.
7. E. R. John, B. Z. Karmel, W. C. Corning, P. Easton, D. Brown, H. Ahn, M. John, T. Harmony, L. Prichep, A. Toro, I. Gerson, F. Bartlett, R. Thatcher, H. Kaye, P. Valdes, E. Schwartz, *Science* **196**, 1393 (1977).
8. See E. R. John in (*1*), p. 74.
9. For the original DEDAAS (Digital Electrophysiological Data Acquisition and Analysis System) we used a PDP 11/10 minicomputer and magnetic tape drives. For the systems used to gather the data described here we used PDP 11/03 microprocessors and floppy disks. The recorded monopolar data were numerically combined to construct the required bipolar derivations. For our initial frequency analyses we used the FFT. Currently, our spectral computations are performed by numerical filtering. The spectral analysis uses a four-pole Butterworth recursive band-pass filter, complex demodulation, and a two-pole recursive low-pass filter to achieve 36 dB/octave filter roll-offs. The results are essentially identical with the FFT, but our present method offers certain computational advantages.
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11. Data on test-retest reliability of the eyes open and eyes closed EEG, on the reliability of absolute power versus relative power estimates of the content of each frequency band in each derivation, comparisons of spectral analyses of visual versus computer editing of artifacts, and the distribution of values observed in various groups of healthy and learning disabled children are presented in detail in E. R. John, H. Ahn, L. Prichep, H. Kaye, D. Brown, P. Easton, B. Z. Karmel, A. Toro, R. Thatcher, *Functional Neuroscience* (Erlbaum, Hillsdale, N.J., in preparation), vol. 4.
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13. In this process, alpha 1 and alpha 2 were combined into a single alpha estimate that was equal to the square root of the sum of alpha 1 squared and alpha 2 squared. Beta 1 and beta 2 were similarly combined into a single beta estimate.
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15. Since the frequency response of our amplifiers, the objective nature of our computer artifact rejection, and the sharpness of our digital filters represented important possible sources of difference from the work of Matoušek and Petersén (*5*), we devised an empirical correction to relate the two data sets. Using a demographically diverse group of 47 normal children, we computed the mean values and standard deviations for each of the 32 EEG parameters, regressing all data to the group mean age of 10.6 years. Small differences were found between the resulting means and the values predicted for that age by the regression equations. For each frequency band, the mean value of this difference was computed across all eight derivations. The resulting calibration constants were −0.28 for delta, −0.07 for theta, +0.17 for alpha, and +0.13 for beta. These constants are added to the zero order term (C_0) of each regression equation related to the corresponding band for any derivation and constitute the appropriate translation of measures made by our methods to those used in constructing the normative tables on which these equations were based. A corresponding calibration procedure must be followed for any system with which these equations are to be used. It is essential to note that any change in apparatus, artifacting methods, or editing criteria obligates the user to recalibrate the overall system and technique.
16. Examining the log transformed normative data further, we found that the values of the standard deviations were strikingly close to a constant, differing with each measure but independent of age. The physical, ethnic, and cultural heterogeneity of the children in our studies is far greater than the carefully screened and relatively homogeneous Swedish group from which the normative tables were derived. Further, the published data (*5*) do not permit accurate computation of standard deviations for relative power. The standard deviations observed in our data were about 1.5 times larger for each EEG parameter than those reported for the Swedish children, perhaps reflecting the greater heterogeneity of our sample. Therefore, it was assumed that the log transformed values of the standard deviations obtained in our 10.6-year age group would be an acceptable approximation across the range of 1 to 21 years described by the equations, pending sufficient data of our own to compute more precise values.
17. It is worthwhile to obtain a precise prediction of the relative power expected in each band, even though the four bands are not independent for this measure, since individuals may display significant deviations in any one of the bands. Further, behavior patterns and clinical implications vary as a function of the frequency band in which significant deviations occur.
18. F. A. Gibbs and E. L. Gibbs, *Atlas of Encephalography*, vol. 3, *Neurological and Psychological Disorders* (Addison-Wesley, Reading, Mass., 1964); O. Eeg-Olafsson, *Acta Paediatr. Scand. Suppl.* **208** (1970).
19. These data were gathered on a control sample of 129 children who were matched by age, grade, gender, and handedness to another sample of 129 children who were exposed to malnutrition in the first year of life. The control sample had never suffered from malnutrition. The study (F. Ramsey, G. Solimano, J. Galler, E. R. John, H. Ahn, S. Lobel, E. Mason, in preparation) was supported by the Ford Foundation grant 770-0471.
20. A high percentage of the children who were "volunteered" for this study by their parents could be considered significantly "at risk" for brain dysfunction based on their medical or behavioral histories, or were classified as underachievers by standardized achievement tests. This high percentage suggests that parents who volunteer their children for such normative studies as ours include a large proportion who are concerned about some aspect of their child's behavior or development. Those who wish to obtain a "normal" sample for normative studies must exercise adequate precautions to screen out such questionable individuals. The basic quandary encountered while constructing norms is whether to exclude those who may well have compensated adequately although apparently at risk, or to include those who are obviously at risk. This decision requires the deliberate choice of either a type I or type II bias of norm construction. We opted for exclusion of all children who were multiply at risk, reasoning that the higher false positive rate resulting from the smaller variance in the data would at worst subject a normal child to more intense scrutiny.
21. The equations for beta in T_3–T_5, T_4–T_6, F_7–T_3, and F_8–T_4 are not significantly different from a constant function. However, to describe the data with the same mathematical formulation and for comparison with the Swedish data, the linear equations are presented.
22. H. Ahn, L. Prichep, E. R. John, H. Baird, M. Trepetin, H. Kaye, *Science* **210**, 1259 (1980).
23. Supported by National Science Foundation grants DAR 78-18772 and APR 76-24662 and by grant G007604516 from the Office of Education, Bureau of Education for the Handicapped. We acknowledge the assistance of A. Toro, L. Valencia, M. Flanders, S. Lobel, and P. Clark with data analysis and K. Tolman in preparation of the manuscript.

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