the neonate and thus a concomitant impairment in thromboxane production.

It is thus clear from the studies to date of arachidonate metabolism in the neonatal platelets that, although subtle differences in arachidonic acid mobilization and total cyclooxygenase activity occur, these differences do not contribute to the marked differences in aggregation and release that have been noted between platelets from the adult *versus* neonate, *i.e.*, the neonatal platelet dysfunction is not "aspirin-like" in nature. Moreover, our present study introduces a new and possible important difference between adult and neonatal plasma, namely the differential response to exogenous arachidonic acid. Since this unsaturated fatty acid is the precursor of a variety of cyclooxygenase and lipoxygenase metabolites including leucotrienes produced by various cellular systems in both the adult and neonate, increased availability of this precursor compound in neonatal plasma may be of clinical importance in a variety of neonatal pathophysiologic states.

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The Influence of Early Malnutrition on Subsequent Behavioral Development. IV. Soft Neurologic Signs

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Summary

Soft neurologic signs were evaluated in 101 Barbadian school children, ages 4–11 years, who were malnourished in the first year of life, and 101 comparison children matched for age, sex, and handedness, but who had no history of malnutrition. Previously malnourished children performed significantly slower than comparison children on several timed motor tasks when using the nondominant hand only. Boys were found to perform significantly slower than girls, and younger (4–7 years of age) children performed slower than older (8–11 years of age) children. A model is presented that displays interrelationships among previous malnutrition, soft neurologic signs, classroom behavior, intelligence, and physical growth. In summary, slow motor performance was associated with lower verbal and performance IQ and the presence of attention deficit disorder, as assessed by the child's teacher. The time to perform the motor tests was unrelated to measures of physical growth.

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Abbreviations

WISC, Wechsler Intelligence Scale for Children
MANOVA, multivariate analysis of variance
MRA, multiple regression analysis

This report is one of a series describing the long-term effects of early malnutrition on the behavioral development of Barbadian school children. The earlier reports in this series demonstrated a modest reduction in IQ among the previously malnourished group (4) and the increased frequency of impaired classroom behaviors, including attention deficit disorder, impaired social skills, emotional instability, and impaired physical appearance (5). These factors resulted in poor school achievement by this group when compared to well-nourished classmates, matched for age, sex, and handedness to the index children (7). Current socioeconomic and household factors also differed in the index and control groups, but did not account for any aspects of the poorer school performance in the malnourished children (4, 5, 7). Although other features of the home, such as maternal morale, the quality of the parent-child relationship, and mother's social and educational interests, were similarly unrelated to impaired school performance, these were closely related with the early episode of malnutrition to which they may have contributed (J. R. Galler, F. Ramsey, and G. Solimano, submitted for publication). Height and weight were also studied in these children and were significantly reduced in the index group, although the rate of growth and the ratio of height to weight were the same as in the control group (6). No other differences were detected on physical examination.

Based on these observations, we have hypothesized a sequence of events in which early malnutrition leads to a permanent expression of behavioral and cognitive impairment, the most prominent of which is expressed as an attention deficit disorder. This syndrome prevents the child from deriving full benefit from environmental and educational opportunities. The outcome is apparently not related to current socioeconomic circumstances and microenvironmental factors in the home, which thus are independent variables associated with malnutrition. In the study reported here, we extend our observations to include soft neurologic signs, namely measures of dysfunction not associated with specific progressive neurologic disease. This evaluation included tests, used earlier by Denckla and her colleagues (1, 2), of handedness and the capacity of school-aged children to perform discriminating motor tasks to examine normal school age children and, later, hyperactive boys. Soft neurologic signs and clumsiness have also been studied by other authors in children at risk for minimal brain dysfunction (8, 9, 12, 13). Although the results have been inconclusive because of methodologic differences between studies, clumsiness in children has in general been associated with a higher rate of school and learning problems. In the current study, we have related soft neurologic signs to classroom behavior, intellectual performance, and physical growth of the malnourished children and to their prior nutritional status, in an attempt to further define the sequence of events leading from the early episode of malnutrition to the long-term deficits with which it is associated. In doing so, our studies throw further light on the significance of soft neurologic signs as diagnostic tools in detecting brain dysfunction.

MATERIALS AND METHODS

Site of Study. The study was conducted at the National Nutrition Centre at the Queen Elizabeth Hospital, Bridgetown, Barbados. This center was established in 1967 to follow the development of all children diagnosed as being malnourished. Since its inception, the center has treated and provided follow-up care for approximately 2100 children. Extensive records of diagnosis, treatment, and follow-up to 12 years of age are available for each child. The availability of these records has allowed us to select a well-documented population of children who had marasmus during the first year of life.

Several other features of this island population were favorable to our investigation. First, health care delivery is good. Almost all children are born in Queen Elizabeth Hospital or allied facilities, and well-documented records of obstetric care are available in almost all cases. Furthermore, children are routinely followed by local clinics and these records were made available for the current study. Second, Barbados has the highest literacy rate in the West Indies (98%), with nearly all children attending school. Third, the population is homogeneous, 95% being blacks of West African origin. Fourth, the country is small and readily accessible so that no group is overlooked. This combination of factors made Barbados an ideal setting for the current study.

Sample Selection. Exposed series (n = 129). Index cases selected for testing were restricted to children aged 4 to 11 years who had been diagnosed with grade II-III marasmus (Gomez Scale) during the first year of life and hospitalized at the Queen Elizabeth Hospital during this episode of protein-energy malnutrition. All children received routine medical care through the National Nutrition Centre after discharge, including home visits by public health nurses, and families were provided with nutrition counseling and subsidized milk. Further episodes of malnutrition in this population are rare and any children with evidence of a second bout of such illness were excluded.

The following criteria were also applied for the selection of the index children. (a) In order to exclude those children exposed to significant intrauterine malnutrition, the birth weight of the infant had to be equal to or greater than 5 lbs. (b) Cases with prenatal or perinatal complications, as measured by standard criteria including the Apgar score, were eliminated to exclude other causes of impaired behavioral development. (c) Children with a history of convulsions, head injury, or loss of consciousness were also excluded.

This information was obtained by reviewing obstetric records of all children followed by the National Nutrition Centre. Of the 141 children who met these criteria, 12 were eliminated as follows: seven cases were lost to follow-up, in four cases parents refused to grant permission for their child to participate, and in one case the child had cerebral palsy.

Nonexposed series (n = 129). The nonexposed (comparison) series met the same criteria applied in the selection of the index series except that these children had no history of protein-energy malnutrition.

To qualify for inclusion, the child was required to have had at least three recorded medical visits in the first year of life, reporting normal growth and development, and two similar reports each year prior to school admission, which is part of the health care service for all Barbadian preschool children. During the school years, growth is measured annually and evidence of normal development was also recorded for the comparison group.

For our study, the comparison children were selected from the same classrooms and schools as the index children whenever possible and they were matched to the index children by age, gender, and handedness. In the few cases where this was not possible because of inadequate health records of children in the class, a child from a neighborhood health care center was selected. This procedure of using schoolmates or neighborhood children was used in order to control for socioeconomic and other environmental differences as much as possible.

Neurological Examination. Two trained pediatricians administered a general neurologic examination, which included evaluation of cranial nerve function, motor strength, sensory responsiveness, and deep tendon reflexes. These did not differ significantly between index and control children and were, in all instances, within normal range for children of this age. In addition to the general neurologic examination, we also tested each child for signs of impaired motor development, also referred to as "soft" neurologic signs. This term implies measures of mild dysfunction, not associated with specific progressive neurologic disease. The evaluation of motor development in our study included measures of handedness and performance of seven motor tasks, and these were assessed by a trained nurse or pediatrician, neither of whom was familiar with the child's history. Since control children had been matched to index cases on the basis of reported handedness, an examination of hand dominance was undertaken in part to verify the accuracy of the sample selection. This was assessed by having the child catch a ball, use a spoon, write his name, cut with scissors, and open a door and noting which hand the child used to perform four of five of these tasks. Performance on the following seven motor tasks were also measured: 1) repetitive movements of one finger; 2) successive finger movements; 3) repetitive hand patting; 4) alternating forearm pronation-supination; 5) alternating hand flexion-extension; 6) repetitive toe-tapping; and 7) heel-toe tapping in rocking motion (1). The quality of performance on the seven motor tasks was evaluated for both the dominant and nondominant hand as follows: 1) time (in seconds) to perform 20 movements on each of the motor tasks (*e.g.*, 10 pairs of pronation-supination or 20 repetitive finger taps); 2) rhythmicity of motion (rated as good or fair or poor); 3) maintenance of sequence (rated as good or fair or poor); and 4) the presence or absence of mirror movements of the opposite limb.

Classroom Behavior and IQ. The procedure and data concerning the WISC and classrooms behaviors in this population have been described in earlier papers of this series (4, 5). IQ was assessed by a psychologist using the WISC modified for Barbados. Classroom behavior was assessed using a 30-item questionnaire administered to teachers of index and control children. Neither the psychologist nor teacher had knowledge of the child's prior medical history and, therefore, was blind.

DATA ANALYSIS

The frequency of right, left, and mixed dominance in index and control children was compared using χ^2 analysis. The quality of performance on the motor tasks was analyzed separately for the dominant and nondominant hands, as follows. The *time* to perform each motor task was analyzed using a three-way MANOVA, with nutritional group by sex by age as the independent variable and the time to complete each motor task as the dependent variable. Significant MANOVAs were supplemented by univariate analyses of variance and Newman-Keuls where appropriate. The frequency of *mirror movements*, difficulty in *maintenance of sequence*, and *rhythmicity* were each analyzed by a three-way MANOVA, nutritional group by sex by age as the grouping variable and composite scores for mirror movements, maintenance of sequence, and rhythmicity as the dependent variables. The composite score for mirror movement was calculated by adding the ratings for mirror movements (present = 1 or absent = 0) on the seven motor tasks and then dividing by seven. Composite scores for maintenance of sequence (poor = 1 or good = 0) and rhythmicity (poor = 1 or good = 0) were similarly calculated.

Finally, a series of canonical correlations was performed in order to determine the relationship between the soft neurologic signs, classroom behavior, intellectual performance, and various measures of physical growth. For each series, significant canonical correlations were supplemented by multiple regression analyses, in order to clarify the interpretation of the canonical variates.

RESULTS

Handedness. Handedness was determined as follows. A child who used his right hand for at least four of five dominance tasks was considered to be right-handed; and similarly, a child who performed four of five tasks with the left hand was considered left-handed. Children who used their right or left hands on fewer than four tasks were considered to have mixed dominance. Using these criteria, 103 index and 110 control children were identified as being right-handed, 12 index and 11 control children were identified as being left-handed, and 14 index and 8 control children were found to have mixed dominance. There were no significant differences in the distribution of dominance between the index and control groups.

Performance on the motor tasks. For these and all subsequent analyses, only data from the 101 matched pairs of right-handed index and control children were used, since the number of left-handed and mixed dominant children was small. Age effects were studied by grouping younger children (4–7 years of age) and older children (8–11 years of age) in order to ensure an adequate number of subjects in each cell. Performance on each of the motor tasks was evaluated by measuring the time to perform each task, the rhythmicity and maintenance of sequence, and the presence or absence of mirror movements while performing the task.

Table 1 summarizes the mean times to perform each of the motor tasks for index and control children. The time required to perform each motor task ranged from about 7 s for the finger-

Table 1. *Mean times (seconds) for performing motor tasks for children with histories of malnutrition and their controls, grouped by sex, age, and limb used to perform motor tasks*

Test and nutritional group	Males				Females			
	4–7 years		8–11 years		4–7 years		8–11 years	
	Right	Left	Right	Left	Right	Left	Right	Left
Successive finger tapping								
Control	15.2 ± 3.98	15.0 ± 3.7	11.6 ± 2.5	11.5 ± 2.6	12.3 ± 2.0	12.8 ± 2.0	9.6 ± 2.5	9.4 ± 1.6
Index	15.5 ± 3.7	15.8 ± 3.6	12.3 ± 5.7	12.0 ± 5.2	13.5 ± 3.5	13.8 ± 4.6	10.4 ± 2.1	10.9 ± 2.4
Toe tapping								
Control	9.4 ± 1.33	9.5 ± 1.58	8.6 ± 1.17	9.0 ± 1.10	9.0 ± 1.02	9.2 ± 1.41	8.2 ± 1.23	8.3 ± 0.92
Index	9.9 ± 2.12	10.5 ± 2.34	9.0 ± 1.70	9.5 ± 1.85	9.1 ± 1.00	9.5 ± 1.43	8.4 ± 0.87	9.0 ± 1.25
Heel-toe tapping								
Control	12.6 ± 2.45	12.5 ± 2.36	11.0 ± 2.75	11.2 ± 2.81	13.8 ± 2.54	14.8 ± 3.07	10.7 ± 3.06	10.5 ± 2.36
Index	14.2 ± 2.89	14.5 ± 3.23	11.2 ± 2.91	11.9 ± 2.99	13.9 ± 3.80	13.7 ± 2.93	11.7 ± 2.94	12.0 ± 2.79
Finger tapping								
Control	7.8 ± 1.21	7.9 ± 1.24	7.3 ± 2.35	7.3 ± 1.63	7.9 ± 1.99	8.0 ± 2.09	6.9 ± 0.77	6.9 ± 0.81
Index	8.0 ± 1.67	8.3 ± 1.68	8.4 ± 3.51	8.3 ± 2.93	7.0 ± 0.95	7.3 ± 1.14	7.3 ± 0.91	7.4 ± 1.10
Hand patting								
Control	7.5 ± 1.83	7.8 ± 1.68	7.7 ± 1.24	7.7 ± 1.26	8.1 ± 0.95	8.1 ± 1.07	7.7 ± 0.92	7.7 ± 0.78
Index	8.6 ± 1.10	8.5 ± 1.10	7.6 ± 1.54	7.7 ± 1.35	8.4 ± 1.10	8.1 ± 1.82	7.6 ± 1.52	7.9 ± 1.07
Arm pronation-supination								
Control	8.1 ± 1.11	8.2 ± 1.14	7.9 ± 1.12	7.8 ± 1.33	8.3 ± 1.12	8.1 ± 0.96	8.2 ± 2.35	7.9 ± 1.40
Index	8.8 ± 2.19	9.0 ± 2.28	8.5 ± 1.87	8.3 ± 1.90	8.8 ± 2.35	8.6 ± 2.42	8.0 ± 1.90	8.2 ± 1.77
Hand flexion-extension								
Control	8.2 ± 1.19	7.9 ± 1.93	7.8 ± 1.17	7.5 ± 1.26	8.1 ± 1.43	8.5 ± 1.17	7.9 ± 1.70	7.7 ± 1.52
Index	8.5 ± 1.99	8.5 ± 2.07	8.8 ± 2.34	8.6 ± 2.50	8.4 ± 1.39	8.3 ± 1.71	7.6 ± 1.73	7.5 ± 1.92

tapping task using the same finger to nearly 16 s for successive finger-tapping tasks. The greatest differences in performance time between index and control children were observed on the more difficult tasks, *i.e.*, those which took longer to do, namely successive finger tapping, toe tapping, and heel-toe rocking. In each instance, index children performed more slowly than control children. As may be seen, all children performed the left-handed tasks at similar or slower rates than the right-handed tasks. The table also shows that boys performed more slowly than girls and that younger children, especially the boys, performed more slowly than older children.

These observations were confirmed by multivariate analyses of variance (nutritional group by sex by age) which showed significant effects of each of the independent variables on the time to perform the motor tasks. A significant effect of nutritional group was present for left hand performance only (F (7, 185) = 2.1; $p < 0.05$). Univariate ANOVA was used to measure each motor task separately (Table 2) and showed that index children performed more slowly than control children on the following left-handed tasks: successive finger tapping, toe tapping, heel-toe rocking, and arm pronation-supination. MANOVA also showed significant sex effects. Boys from both control and index groups performed significantly slower than girls on right-handed (F (7, 183) = 4.16; $p < 0.01$) and left-handed (F (7, 185) = 2.41; $p < 0.05$) tasks. Results of the corresponding univariate ANOVAs are summarized in Table 2. This table shows significant differences between boys and girls to complete the successive finger-tapping and toe-tapping tasks for right and left hands, and finger tapping for the left hand only.

The MANOVAs also confirmed significant age effects for both right- (F (7, 183) = 10.1; $p < 0.01$) and left-handed tasks (F (7, 185) = 9.34; $p < 0.01$). In each case, 4- to 7-year-old children were slower than 8- to 11-year-old children. Table 2 summarizes results of the corresponding univariate ANOVAs for each motor task. Significant age-related differences were present for four of seven right-handed tasks and also four of seven left-handed tasks. These included performance on successive finger tapping, toe tapping, and heel-toe rocking for right and left limbs, hand patting for the right hand only, and pronation-supination for the left arm only. There were no significant interactions for either the MANOVAs or univariate ANOVAs for performance of the motor tasks.

Mirror movements, maintenance of sequence, and rhythmicity were each analyzed by three-way MANOVAs (nutritional group by sex by age) using composite scores for the seven tasks. In contrast to the striking findings reported for the time variable, no significant effects of nutritional group, age or sex, or interactions among these were present for performance on either right- or left-handed tasks on any of these three dependent variables.

Correlation between soft neurologic signs, IQ, and classroom behavior. We have previously reported deficits in both IQ and classroom behavior among the same population of previously malnourished children examined in the current study (4, 5). Briefly, a version of the WISC, modified for use in Barbados, showed about a 12-point reduction in IQ, which was greater among girls than among boys. Classroom behavior was evaluated by teachers using a 30-item questionnaire, modified from Richardson (10). When factors were analyzed, the responses to the questionnaire fell into seven categories, four of which were significantly different for index *versus* control groups, namely Factor 1 (attention deficit disorder), Factor 2 (emotional stability), Factor 3 (social skills), and Factor 4 (physical appearance). In each instance, index children were disadvantaged relative to their matched controls.

Accordingly, a series of canonical correlations were generated comparing IQ and the classroom behavior factor scores for each child with performance on the motor tasks described in this paper. Table 3 shows highly significant relationships between the times to perform the motor tasks with the verbal and performance IQs and the four factors describing the types of classroom behavior for each hand separately. This is confirmed by the overall canonical correlation (R_c) which is presented in the lower right-hand corner of the table. Since these values were significant for both right and left hand performance, a more detailed analysis was undertaken. A series of MRAs were generated. First, each of the motor tasks were separately correlated with the classroom behavior factor scores and the IQ measures (rows). Second, each of the classroom behavior factor scores and IQ measures were correlated separately with the motor task (columns). (Individual Pearson correlations are reported for each of these variables and are presented in the columns beneath each of the behavioral measures.) The MRAs show that the significance displayed by the canonical correlation can be related to strong relationships between performance IQ first and then verbal IQ and attention deficit disorder (Factor 1) with performance on the motor tasks. This applies to the data gathered from right-handed and left-handed tasks. Thus, children with lower performance and verbal IQs and poor attention in the classroom are also poor performers on measures of motor skills, *i.e.*, they are clumsy children.

When the MRAs were calculated with each motor task as the independent variable, and the aggregate of IQ and classroom behavior as the dependent variables, three significant relation-

Table 2. *Significant results of analysis of variance (Nutritional group × sex × age) comparing the performance of previously malnourished children with their matched controls*

Independent variable	Dependent variable	F value: Right hand (*df* = 1189)	F value: Left hand (*df* = 1191)	Comments
Nutritional group	Successive finger tapping	NS*	4.16†	Index children slower than control children
	Toe tapping	NS	8.76‡	
	Heel-toe rocking	NS	5.82†	
	Arm pronation-supination	NS	5.11†	
Sex	Successive finger tapping	17.89§	13.1§	Boys slower than girls
	Toe tapping	7.04‡	6.1†	
	Finger tapping	NS	4.08†	
Age	Successive finger tapping	37.46§	47.47§	4–7-year-olds slower than 8–11-year-olds
	Toe tapping	17.79§	12.03‡	
	Heel-toe rocking	37.51§	35.66§	
	Hand patting	7.03‡	NS	
	Arm pronation-supination	NS	4.32†	

* NS, not significant.
† $P < 0.05$.
‡ $P < 0.01$.
§ $P < 0.001$.

Table 3. *Pearson correlations, MRA, and canonical correlations (R_c) showing relationships between measures of IQ and classroom behavior with soft neurologic signs (n = 202)**

	Measures of behavioral function						
	Performance IQ	Verbal IQ	Attention deficit disorder (Factor 1)	Emotional stability (Factor 2)	Social skills (Factor 3)	Physical appearance (Factor 4)	MRA
Right hand							
Successive finger tapping	−0.3790†	−0.2715†	0.1937†	0.0381	−0.0249	−0.1380‡	0.4075†
Toe tapping	−0.2966†	−0.2131†	0.1465‡	−0.0544	0.0615	−0.0582	0.3205†
Heel tapping	−0.2250†	−0.0728	0.0923	−0.0622	−0.0425	−0.0254	0.2719†
Finger tapping	−0.1244	−0.0978	0.0258	0.0277	−0.0568	0.0459	0.1633
Hand patting	−0.1645‡	−0.0929	0.1046	−0.0548	0.0717	−0.0423	0.1903
Hand flexion-extension	−0.0430	−0.0769	−0.0251	−0.0161	0.0046	−0.0368	0.1006
Arm pronation-supination	−0.0290	0.0039	0.1206	−0.0902	−0.0616	−0.0477	0.1643
MRA	0.4544†	0.3134†	0.2758†	0.1544	0.1496	0.1800	R_c = 0.5097†
Left hand							
Successive finger tapping	−0.4166†	−0.2656†	0.2003†	0.0442	0.0058	0.1443‡	0.4388†
Toe tapping	−0.3429†	−0.1428‡	0.2460†	−0.0368	−0.1106	−0.0678	0.3909†
Heel tapping	−0.2735†	−0.0253	0.1560‡	0.0060	−0.0314	−0.0053	0.3092†
Finger tapping	−0.1487‡	−0.1487‡	0.1213	−0.0161	−0.0293	−0.0295	0.1720
Hand patting	−0.1975†	−0.1111	−0.0124	0.0609	0.0208	0.0796	0.2357
Hand flexion-extension	−0.0940	−0.0667	−0.0287	0.0095	0.0201	−0.0848	0.1428
Arm pronation-supination	−0.0525	−0.0609	0.0800	0.1132	−0.0629	−0.0918	0.1788
MRA	0.4792†	0.3012†	0.3998†	0.1765	0.1572	0.1969	R_c = 0.4787†

* Pearson correlations relate a single dependent variable with a single independent variable. MRA relates a single dependent variable with a linear combination or set of independent variables. Canonical correlations relate a set of dependent variables with a set of independent variables, in this case, all behavioral measures with all motor tasks.
† $p < 0.01$.
‡ $p < 0.05$.

ships emerged, namely successive finger tapping, toe tapping, and heel-toe rocking. These three measures, therefore, appear to be the most predictive of the long-term consequences of malnutrition. Since we have previously reported sex differences in IQ performance (4) and in classroom behavior, notably the high incidence of emotional instability among malnourished boys (5), we repeated all the correlations leading to the canonical analysis controlling for sex and found no substantial differences in the observed relationships.

Since we have previously failed to find any significant relationship between IQ and classroom behavior with current socioeconomic circumstances or other aspects of the home environment (4, 5) (submitted for publication), we did not analyze the relationship between the soft neurologic signs and these measures.

Lack of correlation between soft neurologic signs and height and weight. Since we previously reported that height and weight of the index children were significantly reduced in comparison with control children (6), it was important to determine whether impaired motor performance could be due to delayed physical development. The absence of such a correlation is reported in Table 4, which shows nonsignificant canonical correlations between measures of physical growth and performance of the motor tasks. Since sex differences in growth patterns of previously malnourished children had been reported in this population by us, we repeated the analyses controlling for sex effects, and still found no significant results.

Table 4. *Absence of correlation between measures of physical growth and soft neurologic signs*

	Height percentile	Weight/height percentile	Weight percentile	MRA
Right hand				
Successive finger tapping	−0.0144	−0.0786	−0.0945	0.1219
Toe tapping	0.0322	0.0852	0.0191	0.1356
Heel tapping	−0.0093	0.0069	−0.0055	0.0129
Finger tapping	−0.0403	−0.0186	0.0500	0.0510
Hand patting	0.0073	−0.1552	−0.0687	0.1589
Hand flexion-extension	−0.0850	−0.1013	0.0349	0.1560
Arm pronation-supination	−0.1665	−0.0512	0.1235	0.1864
MRA	0.1867	0.2691	0.2155	R_c = NS*
Left hand				
Successive finger tapping	0.0071	−0.0754	−0.0724	0.1089
Toe tapping	0.0225	−0.0814	−0.0125	0.0928
Heel tapping	0.0139	−0.1017	−0.0706	0.1036
Finger tapping	−0.0124	−0.0487	−0.0359	0.0510
Hand patting	−0.0110	−0.1020	−0.0674	0.1033
Hand flexion-extension	−0.0935	0.0638	0.0221	0.1642
Arm pronation-supination	−0.0707	−0.0621	0.0793	0.0979
MRA	0.1129	0.2034	0.1459	R_c = NS

* NS, not significant.

DISCUSSION

Our previous studies on 129 Barbadian school children with histories of marasmus in the first year of life and their matched controls demonstrated a modestly reduced IQ and impaired

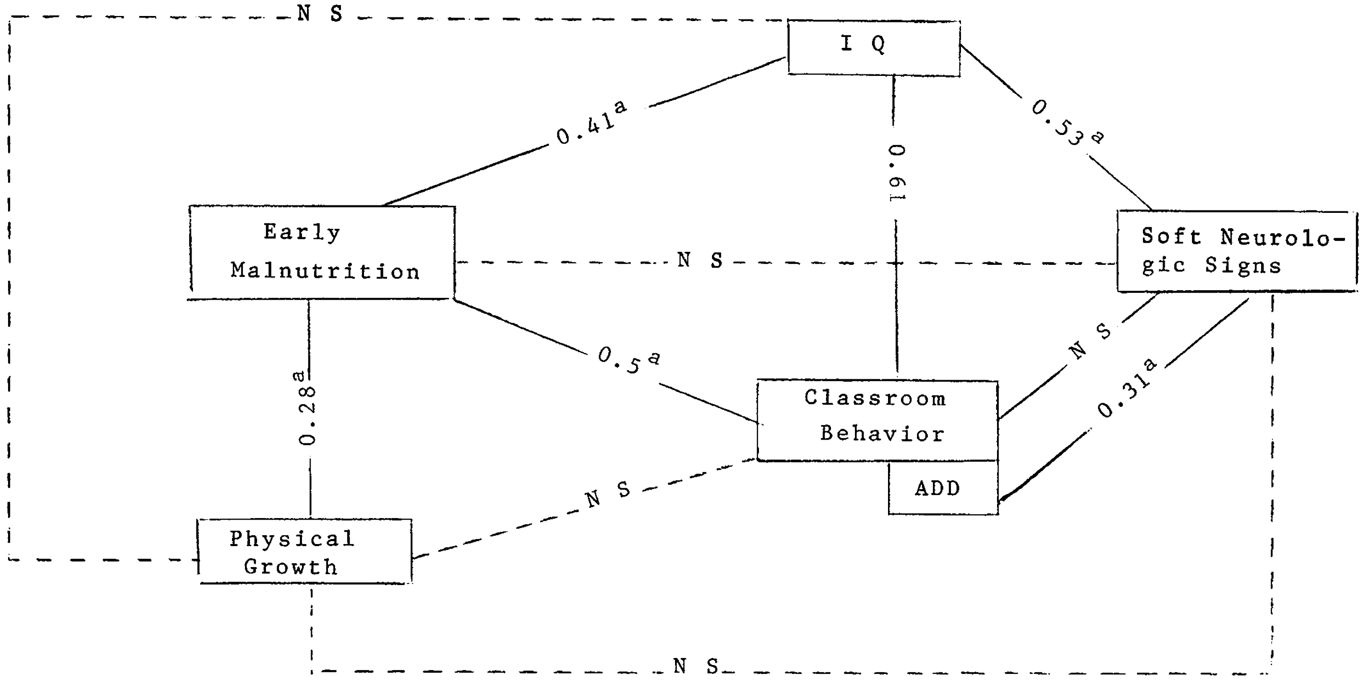

Fig. 1. A multifactorial model of the interrelationships among malnutrition, behavioral development, and soft neurologic signs (*a–c*). *a*, $p < 0.01$. NS, not significant. *b*, the values describing relationships between soft neurologic signs and classroom behavior, physical growth and classroom behavior, and physical growth and soft neurologic signs are canonical correlations for the first significant canonical variate. *c*, all other correlations were calculated using multiple regression analyses. *ADD*, attention deficit disorder.

classroom behavior, the latter being the main impediment to adequate school performance (4, 5, 7). Current socioeconomic conditions and microenvironmental features of the home, though related to the episode of malnutrition, were not found to be directly responsible for impaired school performance at the time of the study (Galler *et al.*, submitted for publication). Height and weight were also reduced in the index group, but the height for weight ratio was unaffected (6).

The present study extends these observations to tests of motor function (soft neurologic signs) in the index and control groups. Three of the seven tests applied were especially sensitive indicators of differences between the two groups, including successive finger tapping, toe tapping, and heel-toe rocking. Among the right-handed children who were studied, performance of tasks by the left hand or foot was especially impaired, and this finding may be clinically relevant as an indicator of developmental delay in evaluating children with previous malnutrition or other insults during the first year of life. Our data also confirm clinical evidence that fine motor skills generally improve with age and are better for girls in this age group. These findings are consistent with those reported by Denckla (1) in a normal United States population and thus suggest cross-cultural validity of these measures of motor function. Figure 1 summarizes the relationship of these new data to our previous studies on the behavioral and cognitive development of previously malnourished children and their physical growth. Reduced performance on the motor tasks for right and left hand combined (soft neurologic signs) was strongly correlated with a reduced full scale IQ (0.53) and to a lesser extent with the attention deficit component of classroom behavior (0.28). These relationships are further elaborated in Table 3. On the other hand, performance of motor tasks for both hands combined was not significantly correlated with a history of previous malnutrition (0.25). This finding is compatible with the data presented in Table 2, namely, the lack of a significant relationship with malnutrition for the right hand tests and a weak ($p < 0.05$) relationship for the left hand. We therefore conclude that the longer time to perform the motor tasks by malnourished children is a consequence of a reduced IQ and, to a lesser extent, deficits in attention rather than being the direct outcome of malnutrition or part of the pathway through which malnutrition results in reduced IQ and classroom behavior. This interpretation of the data is supported by our failure to find other more widespread deficits in brain function such as impaired rhythmicity, sequencing, and the presence of mirror movements.

Finally, our analysis shows that height and weight, which were reduced in the previously malnourished group, were not correlated with either the deficits in motor performance (0.21) or with IQ (0.2) or with classroom behavior (0.16). The significant relationship between physical growth and a previous history of malnutrition (0.28) thus represents an independent effect which cannot account for the reduced motor skills present in previously malnourished children.

A number of early studies have demonstrated the presence of impaired soft neurologic signs in school-aged children with learning problems (2, 11). These findings have been related to conditions early in life such as low birth weight (8). Based on the data presented in this study, early malnutrition should be added as a further possible factor in the etiology of impaired soft neurologic signs and learning disabilities. More rigorous study of the neuropsychologic correlates of early malnutrition is needed. Previously reported studies of the effects of malnutrition on the development of motor skills have been restricted to the period immediately following the episode (3).

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Hypoxia Stimulates Prostacyclin Synthesis by Neonatal Lungs

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Summary

Inhibition of prostaglandin cyclooxygenase augments hypoxic pulmonary vasoconstriction. We used a neonatal lamb lung preparation perfused with Krebs' bicarbonate buffer to characterize and quantify prostanoids produced by the pulmonary vasculature from endogenous arachidonic acid in the absence of formed blood elements during ventilation with normoxic and hypoxic gas mixtures. Prostaglandin (PG) I_2 synthesis increased from 6.4 ± 2.7 ng/min (SEM) during normoxic ventilation to 14.3 ± 5.4 ng/min during hypoxia and returned to 4.7 ± 1.2 ng/min with resumption of normoxia. These data demonstrate that hypoxia stimulates pulmonary vascular synthesis of prostaglandin I_2 from endogenous substrate in neonatal lambs and suggest that the augmentation of hypoxic pulmonary vasoconstriction by prostaglandin cyclooxygenase inhibition is due, at least in part, to interference with the synthesis of this vasodilator prostanoid.

Abbreviations

PG, prostanoid
PGI_2, prostacyclin
TXB_2, thromboxane B_2

Inhibition of prostaglandin cyclooxygenase augments hypoxic pulmonary vasoconstriction in adult mammals of several species (1, 12, 24, 27, 28). A possible explanation for this observation is that hypoxia or hypoxic pulmonary vasoconstriction induces the synthesis of a vasodilator PG that reduces the vasoconstriction. Inhibition of PG synthesis would remove this vasodilator PG and, thus, increase the hypoxic constriction. Indirect evidence supporting this hypothesis in the neonate includes the observations that: 1) PGI_2 is the most abundant PG produced by fetal bovine pulmonary arterial slices (22); 2) under normoxic conditions, PGI_2 is the most abundant PG produced by the newly ventilated neonatal lamb lung (10, 11); 3) PGI_2 is a pulmonary vasodilator in the fetal and neonatal lamb (3, 9, 13), and its vasodilatory effect on the neonatal pulmonary vasculature is more evident during hypoxic pulmonary vasoconstriction (13); and 4) hypoxic pulmonary vasoconstriction in premature and term neonatal goats is augmented by indomethacin, an inhibitor of PG synthesis (23). In the present study, we used a neonatal lamb lung preparation perfused with Krebs' bicarbonate buffer to characterize and quantify prostanoids produced by the pulmonary vasculature from endogenous arachidonic acid in the absence of formed blood elements. Pulmonary perfusate was collected during ventilation with normoxic and hypoxic gas mixtures. Analysis of these perfusates allowed determination of the effect of hypoxic pulmonary vasoconstriction on pulmonary vascular prostanoid synthesis.

MATERIALS AND METHODS

Animal preparation. Fourteen neonatal lambs [10.7 ± 2.0 days old (SEM); 5.5 ± 1.6 kg) were anesthetized with 50 mg/kg α-chloralose IV. A tracheostomy was performed, and ventilation with room air was begun using a constant volume ventilator. A left thoracotomy was performed and the left lung was removed, leaving the mediastinum intact. Consequently, the right lung, which was to be perfused, was not exposed to the environment. The tidal volume was reduced by approximately 40%, the ductus arteriosus was ligated, and the left atrium was cannulated with a Teflon catheter. A repeat dose of 10 mg/kg α-chloralose was administered, and the pulmonary artery was ligated and cannulated, thus sacrificing the animal. Perfusion of the lung with 37°C Krebs' bicarbonate buffer, pH 7.4, containing 2 g glucose/liter equilibrated with 3% O_2, 5% CO_2, 92% N_2 was then begun using

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