Chronic Physiologic Instability Is Associated With Neurodevelopmental Morbidity at One and Two Years in Extremely Premature Infants

Frank R. Mattia, MD, and Raye-Ann O. deRegnier, MD

ABSTRACT. Objective. The objective of this study was to evaluate the relationships between chronic physiologic instability, as assessed by the cumulative daily Score for Neonatal Acute Physiology (SNAP), and neurodevelopmental morbidity in premature infants at 1 year and at 2 to 3 years of age.

Design. The subjects of this retrospective study were extremely premature (≤30 weeks’ gestational age [GA]) infants born in 1993 and 1994 who were seen in follow-up at least once between 1 and 3 years of age. Cumulative daily SNAP scores were calculated over the entire neonatal intensive care unit course for 96 infants (mean GA, 27.3 ± 1.6 weeks; mean birth weight, 1665 ± 270 g). The Mental and Psychomotor Developmental (MDI and PDI) of the Bayley Scales of Infant Development (II) were administered at 1 year and at 2 to 3 years of age; the Receptive–Expressive Emergent Language Scale (REEL) was administered at 2 to 3 years of age.

To compare the most stable infants with the most unstable infants, the subjects were divided into three quartile groups based on their cumulative SNAP scores (<25th percentile, 25 to 75th percentile, and >75th percentile). MDI, PDI, and REEL scores were compared for the three groups using analysis of variance. To evaluate the relative contributions of physiologic stability, intracranial abnormalities, GA, and early postnatal nutritional intakes, multiple regression analyses were performed using cumulative SNAP score, an intraventricular hemorrhage (IVH) score (incorporating IVH and periventricular leukomalacia), GA, and a weight-change score for the first month as independent variables, and MDI, PDI, and REEL quotients as dependent variables. Regression analyses were repeated, with cumulative SNAP subscores for oxygenation, hypotension, acidosis, and hypoxia/ischemia included with IVH score, GA, and first month weight z score change as independent variables, and MDI, PDI, and REEL quotients as dependent variables.

Results. The infants with the highest degree of physiologic instability (cumulative SNAP scores greater than the 75th percentile) had significantly lower MDI scores at 1 year of age and lower PDI scores at 1 year and at 2 to 3 years of age than did infants who were more physiologically stable.

Sixty-seven percent of infants with cumulative SNAP scores greater than the 75th percentile had neurodevelopmental abnormalities at 2 to 3 years of age (cerebral palsy or delayed mental, motor, or language development). Using multiple regression analyses, higher cumulative SNAP scores, IVH scores, and GA were associated with lower 1-year MDI scores. Higher cumulative SNAP scores and IVH scores were associated with lower 1-year PDI scores. By 2 years, only higher cumulative SNAP scores were significantly associated with lower MDI and PDI scores. With respect to language development, only lower weight-change scores over the first month were significantly associated with poorer receptive language development. Lower weight-change scores over the first month and higher hypotension scores were significantly associated with poorer expressive language development. In the secondary regression analyses, higher IVH score, higher cumulative oxygenation scores, and higher hypoxia/ischemia scores all were significantly associated with lower 1-year MDI scores. By 2 to 3 years of age, only higher oxygenation scores were significantly associated with lower MDI scores.

Conclusions. Prolonged physiologic instability was associated with deleterious neurodevelopmental consequences for extremely premature infants through 2 to 3 years of age, independent of effects of intracranial abnormalities and GA. Pediatrics 1998;102(3). URL: http://www.pediatrics.org/cgi/content/full/102/3/e35; extreme prematurity, SNAP score, neurodevelopmental outcome.

ABBREVIATIONS. CLD, chronic lung disease; SNAP, Score for Neonatal Acute Physiology; GA, gestational age; BW, birth weight; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia; PDA, patent ductus arteriosus; NEC, necrotizing enterocolitis; SD, standard deviation; MDI, Mental Developmental Index; PDI, Psychomotor Developmental Index; REEL, Receptive–Expressive Emergent Language Scale; ANOVA, analysis of variance.

Extremely premature infants are at risk for neurodevelopmental morbidity, including developmental delays, cerebral palsy, and neurosensory impairments. These outcomes are not entirely attributable to clinically discernible neuropathology, because it is well documented that premature infants with normal neuroimaging findings also are at risk for these conditions. Neurodevelopmental morbidity has been associated with specific risk factors such as chronic lung disease (CLD), but information is limited regarding mechanisms linking neonatal illness with brain development and function and, in turn, with long-term outcomes. It has been particularly difficult to link cognitive morbidity with specific neonatal diagnoses. The mechanisms through
which heterogeneous types of neonatal illnesses lead to adverse outcomes for some premature infants may have a unifying theme. For example, physiologic derangements such as hypoxia and hypotension during the neonatal period may occur during a variety of disparate illnesses and may lead to brain injury or abnormal brain development.14,20 Scoring systems have been developed recently to objectively grade neonatal illness severity.16–25 These physiologic stability indices are measures of acute instability and are typically obtained on the first day of life and have most often been used as predictors of neonatal mortality.16,17,19–25 Scoring systems also may be useful in understanding the etiology of neurodevelopmental sequelae in preterm infants because they include factors known to cause brain injury (eg, acidosis, jaundice, hypotension). Of the scoring systems, the Score for Neonatal Acute Physiology (SNAP) is best suited for this purpose because it is the most physiologically based and measures instability in several organ systems.

The purpose of this retrospective study was to quantify chronic physiologic instability using the SNAP score and to determine whether there was an association between SNAP scores and adverse neurodevelopmental outcomes in extremely premature infants.

METHODS

Study Design

This study was a retrospective chart review.

Subjects

Subjects were inborn infants ≤30 weeks’ gestational age (GA). GA was determined using best obstetric criteria (mother’s date, last menstrual period, or early ultrasound) and confirmed with physical examination. Infants were included if they were born between January 1, 1993, and December 31, 1994, treated at our level III neonatal intensive care unit, and seen in the follow-up clinic at least once between 1 and 3 years of age. During the 2-year study period, there were 173 inborn admissions of ≤30 weeks’ GA. Of these, 15 (8.7%) died before discharge, 6 (3.5%) died after discharge, 49 (28.3%) were lost to follow-up by 1 year of age, and 7 (4.0%) were followed elsewhere. The remaining 96 infants met the study criteria. GA of the study infants ranged from 23 to 30 weeks’ gestational age (GA). Of these, 15 (8.7%) died before discharge, 6 (3.5%) died after discharge, 49 (28.3%) were lost to follow-up by 1 year of age, and 7 (4.0%) were followed elsewhere. The remaining 96 infants met the study criteria. GA of the study infants ranged from 23 to 30 weeks’ gestational age (GA). Mean GA was 28.1 ± 1.6 weeks, and mean BW was 1193.9 ± 270 g. For the 56 surviving infants who were not included in the study, mean GA was 28.1 ± 1.8 weeks, and mean BW was 1193.9 ± 314.4 g. The nonstudied infants had a 12.5% incidence of significant intracranial abnormalities (grades 3 to 4 intraventricular hemorrhage [IVH], persistent echodensities, cystic periventricular leukomalacia [PVL]).

All infants underwent routine cranial ultrasonography at least twice during their hospital course. The first ultrasonogram was obtained at 5 to 7 days and the second at 1 month. Suspect or abnormal findings were followed more frequently. Ultrasonograms were obtained and read by two experienced pediatric radiologists using a 10-MHz ultrasound transducer. The radiologists each performed at least 250 cranial ultrasonography examinations per year. To provide consistency in reading ultrasonograms, each radiologist peer-reviews the other’s findings periodically. IVH was graded on a scale of 1 to 4 according to the Papile system;12 radiologist peer-reviews the other’s findings periodically. IVH per year. To provide consistency in reading ultrasonograms, each performed at least 250 cranial ultrasonography examinations were obtained and read by two experienced pediatric radiologists.

The clinical characteristics of the subjects are presented in Table 1.

Score for Neonatal Acute Physiology (SNAP)

The SNAP score was used as a standardized assessment of neonatal illness severity.21 It comprises of 28 parameters that include vital signs and laboratory values.

Because potentially significant physiologic instability may not always occur on the first day, the SNAP score was recorded sequentially for each day of the infant’s hospital stay. The area under the curve of a graph plotting a subject’s daily SNAP scores versus time (in days) was calculated to create a cumulative SNAP score (Fig 1). Some modifications of the SNAP score were made to use the SNAP score on infants when they were not acutely ill.

First, to measure oxygenation long-term, without depending solely on arterial blood gas values, the hypoxia score was changed to use either arterial blood gas values or pulse oximetry readings, based on the hemoglobin–oxygen dissociation curves for fetal hemoglobin.26 All infants were monitored with a pulse oximeter until weaned from supplemental oxygen and diuretics for several days, and until moderate to severe apnea of prematurity had resolved. Nurses in the neonatal intensive care unit record oxygen saturation values hourly. The worst value (either PaO2 or pulse oximetry) recorded on each day was scored using the following modification of the SNAP criteria: 0 = normal (eg, PaO2 > 65 mm Hg or worst O2saturation > 90%); 1 = central apnea (eg, PaO2 = 50 to 65 mm Hg or worst O2saturation 85% to 90%); 2 = low O2 saturation (eg, PaO2 = 30 to 50 mm Hg or worst O2saturation 75% to 85%); and 5 = life-threatening (eg, PaO2 < 30 mm Hg or worst O2saturation < 75%).

Second, SNAP scores used the worst values recorded on each day; however, all laboratory parameters were not necessarily recorded every day. Values were extrapolated between recorded values whenever possible. For example, if a subject had a hematocrit score meeting a daily SNAP score of 1 point on hospital day 20 and had a similar hematocrit score recorded on day 25 (with no transfusions being given in the interim), 1 SNAP point would be assigned for hematocrit score on each intervening day. This was done for hematocrit, blood urea nitrogen, creatinine, direct bilirubin, sodium, potassium, and serum bicarbonate measures.

Acute hypoxia, hypotension, and acidosis have been correlated with later neurodevelopmental morbidity.27 Global hypoxia–ischemic events may have different ramifications than isolated disturbances of oxygenation, blood pressure, and acid-base status. To evaluate chronic effects of these abnormalities, cumulative SNAP subscores were created for oxygenation, hypotension, and acidosis (Table 2). If an infant met criteria for only one of these subscores on a given day, that score was recorded as the oxygenation, hypotension, or acidosis score. If SNAP points were assigned for more than one of these parameters (eg, oxygenation score and hypotension), points in those categories were totaled and the subscore for that day was recorded as “hypoxia/ischemia.”

Growth Measures

Weight was recorded at birth and 1 month and converted to standard deviation (SD) units above and below the mean for corrected age (z scores) using standard growth curves.28 To estimate the effect of postnatal nutritional intake, a “weight-change” score was made for each infant by subtracting the 1-month z score weight from the BW z score. A “weight-change” score of 1 indicates that the weight dropped by 1 SD unit from birth to 1 month.

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Clinical Characteristics of the Subjects (N = 96)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Significant intracranial abnormality*</td>
<td>15</td>
</tr>
<tr>
<td>CLD</td>
<td>32</td>
</tr>
<tr>
<td>NEC</td>
<td>10</td>
</tr>
<tr>
<td>PDA</td>
<td>28</td>
</tr>
<tr>
<td>Sepsis</td>
<td>34</td>
</tr>
</tbody>
</table>

*Significant intracranial abnormality is defined as grade 3 or grade 4 IVH, persistent echodensity, or PVL.
impaired neuromotor function. Isolated low or high muscle tone abnormalities in muscle tone, position, and posture attributable to considered to have cerebral palsy if they exhibited persistent physical therapists were unaware of the infants’ SNAP scores and standard pediatric neurologic examinations performed by a neonatologist confirmed all diagnoses of cerebral palsy. All infants in this study had spastic forms of cerebral palsy. The Mental and Psychomotor Developmental Indices (MDI and PDI) of the Bayley Scales of Infant Development (II) were administered to the subjects at 1 year and at 2 to 3 years’ adjusted age. Pediatric occupational or physical therapists performed the Bayley II evaluations. The MDI and PDI were adjusted for prematurity. Infants were considered to have developmental delays if one or more of the following outcomes were noted: MDI or PDI score <70 at 2 to 3 years of age, cerebral palsy, and/or language delay (REEL quotient <0.75).

Neurodevelopmental Follow-up

All subjects were followed at least once. Of the subjects, 6.2% did not have a 1-year follow-up evaluation but were seen at 2 to 3 years, and 17.7% of the subjects did not have a 2- to 3-year follow-up but were seen at 1 year. The adjusted age at the time of follow-up was used. For those seen at the 2- to 3-year follow-up, the mean adjusted age at the time of the evaluation was 26.1 ± 4.0 months.

Neurodevelopmental follow-up of the subjects included standard pediatric neurologic examinations performed by a neonatologist and pediatric occupational or physical therapist from the neonatal intensive care unit follow-up clinic. The occupational and physical therapists were unaware of the infants’ SNAP scores and were not involved in the neonatal care of the infants. Infants were considered to have cerebral palsy if they exhibited persistent abnormalities in muscle tone, position, and posture attributable to impaired neuromotor function. Isolated low or high muscle tone in the absence of other abnormal findings was not considered to be cerebral palsy. A pediatric physiatrist or developmental pediatrician confirmed all diagnoses of cerebral palsy. All infants in this study had spastic forms of cerebral palsy.

The Mental and Psychomotor Developmental Indices (MDI and PDI) of the Bayley Scales of Infant Development (II) were administered to the subjects at 1 year and at 2 to 3 years’ adjusted age. Pediatric occupational or physical therapists performed the Bayley II evaluations. The MDI and PDI were adjusted for prematurity. Infants were considered to have developmental delays if their corrected MDI or PDI scores were >2 SD units below the mean (ie, a corrected score <70). Because scores ≤50 cannot be assigned, MDI and PDI scores ≤50 were recorded as having a value of 49. One subject was tested with the earlier edition of the Bayley, and his 1-year MDI and PDI scores were not included in our analyses.

The Receptive–Expressive Emergent Language Scales (REEL) were administered at 2 to 3 years of age. REEL scores were expressed as age equivalents. To standardize for unequal ages at testing, REEL quotients were created by dividing the age equivalent of the REEL score by the subject’s age corrected for prematurity. Receptive and expressive language delays were considered to be present if the REEL quotient was ≤0.75, which at 2 years’ adjusted age would indicate a delay of 6 months or more.

Subjects were classified as having neurodevelopmental abnormalities if one or more of the following outcomes were noted: MDI or PDI score <70 at 2 to 3 years of age, cerebral palsy, and/or language delay (REEL quotient <0.75).

Data Analyses

StatView 4.5 (Abacus Concepts, Inc, Calabasas, CA) was used for data analysis. To compare neurodevelopmental outcomes for the most stable infants with outcomes for the most unstable infants, subjects were divided into three groups based on quartiles of the cumulative SNAP score: <25th percentile; 25th to 75th percentile; and >75th percentile (Table 3). The 1- and 2-year MDI and PDI scores, as well as the REEL quotients, were compared across the three quartile groups using analysis of variance (ANOVA). Significant results were followed up with Bonferroni corrected t tests.

To compare neurodevelopmental abnormalities (as defined previously) among the three quartile groups, the number of infants in each group with one or more neurodevelopmental abnormalities was compared using χ² tests. Significant results were followed with post hoc χ² tests. Using the Bonferroni adjustment for multiple comparisons, significant values were those for which the P value was <0.017.

Neonatal factors not included in the SNAP score may have effects on neurodevelopmental outcome including intracranial abnormalities, nutritional status, and GA. To evaluate further the relative importance of these variables, multiple regression analyses were conducted using cumulative SNAP score, IVH score, GA, and first month weight-change z score as independent variables, and MDI, PDI, and REEL quotients as dependent variables. Regression analyses were repeated, with cumulative SNAP subscores for oxygenation, hypotension, acidosis, and hypoxia/ischemia included with IVH score, GA, and first month weight-change z score as independent variables, and MDI, PDI, and REEL quotients as dependent variables.

RESULTS

Those infants with cumulative SNAP scores above the 75th percentile had significantly lower MDI scores at 1 year (ANOVA; P < .0001) and lower PDI scores at 1 year (ANOVA; P < .0001) and at 2 to 3 years (ANOVA; P < .0004) than did infants in the other quartile groups (Figs 2 and 3). There were no
significant differences noted among the groups when comparing REEL quotients.

At 2 to 3 years’ adjusted age, infants with cumulative SNAP scores greater than the 75th percentile had a higher incidence of cerebral palsy, as well as delayed mental and motor development, compared with infants in the other quartile groups (Table 4).

Two thirds of the infants with cumulative SNAP scores greater than the 75th percentile had at least one neurodevelopmental abnormality.

In multiple regression models (Table 5), higher cumulative SNAP scores, IVH scores, and GA were significantly associated with lower 1-year MDI score.

By 2 to 3 years of age, only higher cumulative SNAP scores were significantly associated with lower MDI and PDI scores.

**TABLE 3.** Cumulative SNAP Score Quartile Groups

<table>
<thead>
<tr>
<th>Quartile</th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of infants</td>
<td>&lt;25th Percentile</td>
<td>24</td>
<td>25–75th Percentile</td>
</tr>
<tr>
<td>Cumulative SNAP score range</td>
<td>43–128</td>
<td>136–342</td>
<td>354–1177</td>
</tr>
<tr>
<td>Median cumulative SNAP score</td>
<td>98</td>
<td>244</td>
<td>438</td>
</tr>
<tr>
<td>Mean GA ± 1 SD unit (weeks)</td>
<td>28.8 ± 1.0</td>
<td>27.0 ± 1.5</td>
<td>26.5 ± 1.6</td>
</tr>
<tr>
<td>Mean BW ± 1 SD unit (g)</td>
<td>1276 ± 288</td>
<td>1046 ± 227</td>
<td>884 ± 182</td>
</tr>
<tr>
<td>Weight change ± SD</td>
<td>-1.227 ± 0.877</td>
<td>-1.802 ± 1.042</td>
<td>-1.604 ± 0.834</td>
</tr>
<tr>
<td>Significant intracranial abnormality, n (%)</td>
<td>1 (4.2%)</td>
<td>7 (14.3%)</td>
<td>7 (30.4%)</td>
</tr>
<tr>
<td>CLD</td>
<td>0 (0)</td>
<td>14 (28.6)</td>
<td>18 (78.3)*</td>
</tr>
<tr>
<td>NEC</td>
<td>1 (4.2)</td>
<td>5 (10.2)</td>
<td>4 (17.4)</td>
</tr>
<tr>
<td>PDA</td>
<td>3 (12.5)</td>
<td>16 (32.7)</td>
<td>9 (39.1)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>1 (4.2)</td>
<td>16 (32.7)</td>
<td>17 (73.9)*</td>
</tr>
</tbody>
</table>

* Significant differences between group III and groups I and II.

**Fig 2.** First- and second-year MDI scores (mean ± 1 SD unit) for each of the cumulative SNAP quartile groups. * Significant difference (P < .05) among MDI scores of infants with cumulative SNAP scores above the 75th percentile and MDI scores of infants in the two other groups.

**Fig 3.** First- and second-year PDI scores (mean ± 1 SD unit) for each of the cumulative SNAP quartile groups. * Significant difference (P < .05) among PDI scores of infants with cumulative SNAP scores above the 75th percentile and PDI scores of infants in the two other groups.
scores were significantly associated with lower MDI scores. Weight change over the first month was not associated with 1-year or 2- to 3-year MDI.

With respect to motor development, higher cumulative SNAP scores and IVH scores were significantly associated with lower 1-year PDI scores (Table 5). By 2 to 3 years of age, only higher cumulative SNAP scores were significantly associated with lower PDI scores.

With respect to language development, higher cumulative SNAP score and lower weight-change z scores over the first month were significantly associated with poorer receptive language development. Lower weight-change z scores over the first month and higher hypotension scores were significantly associated with poorer expressive language development (Table 6).

**DISCUSSION**

The results of this study demonstrated that increasing levels of chronic physiologic instability were associated with diminished mental, motor, and receptive language development through 2 years of age in extremely premature infants, independent of the effects of severe intracranial abnormalities and of GA.

In the present study, both a cumulative index of physiologic derangements (encompassing mild and severe events) and an index of intracranial abnormalities were used as cofactors in the regression analyses. Both factors were found to have significant effects on development at 1 year of age, but by 2 years of age, only the cumulative SNAP score had statistically significant effects. This suggests that the physiologic factors predisposing to intracranial hemorrhage and PVL may have more lasting ramifications on the developing nervous system than does the CNS lesion itself.

The results of the study add to a growing body of evidence that acute and chronic neonatal physiologic abnormalities do have a lasting impact on development. Brazy et al developed the Nursery Biologic Risk Score, a scoring system designed to focus on mechanisms of brain injury for very low BW infants. This score is not a physiologic scoring system per se,

**TABLE 4.** Incidence of Neurodevelopmental Abnormalities at 2 to 3 Years for Each Cumulative SNAP Score Quartile Group

<table>
<thead>
<tr>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;25th Percentile</td>
<td>25-75th Percentile</td>
<td>&gt;75th Percentile</td>
</tr>
<tr>
<td>n = 17/24</td>
<td>n = 42/49</td>
<td>n = 21/23</td>
</tr>
<tr>
<td>Any neurodevelopmental abnormality, n (%)</td>
<td>5 (29.4)</td>
<td>12 (28.6)</td>
</tr>
<tr>
<td>2-Year MDI &lt; 70</td>
<td>0 (0.0)</td>
<td>5 (11.9)</td>
</tr>
<tr>
<td>2-Year PDI &lt; 70</td>
<td>2 (11.8)</td>
<td>4 (9.5)</td>
</tr>
<tr>
<td>REEL (receptive) &lt; 0.75</td>
<td>1 (5.9)</td>
<td>8 (19.0)</td>
</tr>
<tr>
<td>REEL (expressive) &lt; 0.75</td>
<td>2 (11.8)</td>
<td>5 (11.9)</td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td>1 (5.9)</td>
<td>3 (7.1)</td>
</tr>
</tbody>
</table>

**TABLE 5.** Multiple Regression of Significant Predictors of MDI, PDI, and REEL Scores

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Variable</th>
<th>Partial R2</th>
<th>t Value</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Year MDI</td>
<td>Cumulative SNAP</td>
<td>.33</td>
<td>−5.54</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td></td>
<td>IVH</td>
<td>.08</td>
<td>−3.13</td>
<td>.0024</td>
</tr>
<tr>
<td></td>
<td>GA</td>
<td>.05</td>
<td>−2.23</td>
<td>.0429</td>
</tr>
<tr>
<td>1-Year PDI</td>
<td>Cumulative SNAP</td>
<td>.25</td>
<td>−4.97</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td></td>
<td>IVH</td>
<td>.12</td>
<td>−3.97</td>
<td>.0002</td>
</tr>
<tr>
<td>2 to 3-Year MDI</td>
<td>Cumulative SNAP</td>
<td>.13</td>
<td>−2.53</td>
<td>.0136</td>
</tr>
<tr>
<td></td>
<td>IVH</td>
<td>.21</td>
<td>−3.29</td>
<td>.0023</td>
</tr>
<tr>
<td>REEL (receptive)</td>
<td>Cumulative SNAP</td>
<td>.10</td>
<td>−2.43</td>
<td>.0179</td>
</tr>
<tr>
<td></td>
<td>Weight change</td>
<td>.07</td>
<td>2.33</td>
<td>.0227</td>
</tr>
<tr>
<td>REEL (expressive)</td>
<td>Weight change</td>
<td>.08</td>
<td>2.50</td>
<td>.0148</td>
</tr>
</tbody>
</table>

**TABLE 6.** Multiple Regression of Significant Predictors of MDI, PDI, and REEL Scores

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Variable</th>
<th>Partial R2</th>
<th>t Value</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Year MDI</td>
<td>IVH</td>
<td>.12</td>
<td>−3.58</td>
<td>.0006</td>
</tr>
<tr>
<td></td>
<td>Oxygenation score</td>
<td>.09</td>
<td>−2.81</td>
<td>.0062</td>
</tr>
<tr>
<td></td>
<td>Hypoxia/ischemia</td>
<td>.06</td>
<td>−2.22</td>
<td>.030</td>
</tr>
<tr>
<td>1-Year PDI</td>
<td>IVH</td>
<td>.17</td>
<td>−4.10</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td></td>
<td>Oxygenation score</td>
<td>.14</td>
<td>−3.80</td>
<td>.0003</td>
</tr>
<tr>
<td>2 to 3-Year MDI</td>
<td>Oxygenation score</td>
<td>.07</td>
<td>−2.03</td>
<td>.047</td>
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<tr>
<td></td>
<td>IVH</td>
<td>.11</td>
<td>−2.45</td>
<td>.0174</td>
</tr>
<tr>
<td></td>
<td>Hypotension</td>
<td>.04</td>
<td>−2.27</td>
<td>.027</td>
</tr>
<tr>
<td>REEL (receptive)</td>
<td>Weight change</td>
<td>.05</td>
<td>2.05</td>
<td>.045</td>
</tr>
<tr>
<td>REEL (expressive)</td>
<td>Weight change</td>
<td>.06</td>
<td>2.29</td>
<td>.0254</td>
</tr>
<tr>
<td></td>
<td>Hypotension</td>
<td>.07</td>
<td>−2.26</td>
<td>.0217</td>
</tr>
</tbody>
</table>

**Note:** Significant difference between group III and group II. * Significant difference between group III and group I. n indicates number of infants in each group seen at 2 to 3 years in follow-up.
but includes a combination of acute physiologic derangements and known neuropathology. Using this score, the authors determined that blood pH and hypoglycemia were physiologic indicators of abnormal development, in addition to the presence of IVH, PVL, seizures, infection, and mechanical ventilation. In a follow-up to this study, Goldstein and colleagues evaluated the association between developmental outcomes and acute episodes of hypoxia, hypotension, and acidosis (as defined using the Nursery Biologic Risk Score). The authors demonstrated that severe acute metabolic acidosis was most associated with neurodevelopmental morbidity. Gaudier and colleagues found that low umbilical cord pH and metabolic acidosis were significant predictors of impairment in infants weighing <1000 g at birth.

Conflicting results were obtained by Needleman, Vance, and Kelly-Vance, who investigated the association between first-day SNAP scores and scores on the Bayley Scales of Infant Development through 24 months in infants weighing <1500 g. They found no significant association between the first-day SNAP score and the Bayley MDI or PDI for the 32 infants followed. This absence of a significant effect may be attributable to the relatively small size of the cohort followed. It also may reflect that the first-day SNAP score does not necessarily provide an accurate representation of the entire hospital course of a premature infant. In the present study, the first-day SNAP score represented the worst day for only 49% of the subjects.

Most of the studies performed to date have indicated that acute physiologic derangements are associated with adverse effects on infant development in premature infants. The conflicting nature of some reports may simply reflect the capacity of infants to recover from single events if they do not suffer permanent damage during the event and if they subsequently stabilize. Indeed, most infants who suffer from hypoxic-ischemic insults will recover. However, persistent, recurrent, or patterned insults, even if subtle, may have deleterious ramifications for processes that occur over long periods, such as the growth and development of the premature infant’s brain.

Development of the premature brain after 23 weeks of gestation is a complex orchestration of interrelated processes in various stages of completion, including neuronal differentiation, synaptogenesis, gliogenesis, and the last phases of neuronal migration. In this complicated cascade of events, the timing of an insult could be crucial in terms of its ultimate effect. A repetitive or chronic change in the cellular environment attributable to ongoing physiologic abnormalities (such as hypoxia, acidosis, hypoglycemia, and hyperbilirubinemia) may create an environment that is not conducive to recovery from acute severe brain insults or from a series of lesser insults. Superimposed on these processes are the increased nutritional and metabolic requirements of an unstable neonate. Although more pressing metabolic needs are being met elsewhere, the developing central nervous system may be undernourished, leading to sequelae such as poor myelination or decreased synaptogenesis, which may have functional outcomes. This is supported by the findings of the present study, which documented that infants with the poorest weight gain during the first month had slower language development at 2 to 3 years of age.

The study also found that worsening oxygenation scores were associated with decreased mental development through 2 years of age. Conventional wisdom dictates that isolated hypoxia is a relatively benign event for the neonate and that hypoxic-ischemic events are more pathogenic. Goldstein and colleagues did not find an effect of acute hypoxic episodes on the development of very low BW infants. Although it is known that newborn infants can withstand severe episodes of hypoxia for longer periods than can adults, at least in terms of neuronal cell death, the developing brain may not tolerate the frequent fluctuations in oxygenation that are common in unstable premature infants.

At least one other study has described an association between oxygenation and mental development in premature twins. Raz and colleagues demonstrated that twins with oxygen requirements minimally higher than those of their more stable siblings had significantly lower MDI scores on follow-up evaluation. This association was magnified by prematurity.

If hypoxia per se does not cause neuronal cell death, then we must speculate on an alternative mechanism to explain the association noted in this study between hypoxia and mental development in premature infants. Fluctuating oxygen levels, not hypoxia or hyperoxia alone, are currently thought to be the mechanism for the development of retinopathy of prematurity, and this same mechanism might pertain to developing brain vascularity as much as retinal vascularity. Alternatively, fluctuating oxygen levels might alter key steps in brain development. This could apply particularly to synaptogenesis, which has a high metabolic demand and which becomes an exponential growth process after 28 weeks of gestation. A prospective study comparing cognitive outcomes of infants randomized to different methods of managing oxygenation might clarify the relationship between recurrent episodes of hypoxia and brain development.

There are some inherent limitations in using any of the physiologic scoring systems currently available to evaluate risk for neurodevelopmental impairments. Some types of potentially relevant physiologic disturbances are not included in the SNAP score. For example, respiratory alkalosis is postulated to cause brain injury, but it is not included in the SNAP score. Also, the SNAP score includes items that may have no apparent effects at all on development, such as white blood cell counts. Other SNAP items may have different effects at different times during the course of a long neonatal intensive care unit stay (eg, high indirect bilirubin, low hemoglobin). However, we did not alter the SNAP score to address these concerns because various factors may interact with each other in unanticipated ways. As an example, anemia alone may have no effects on de-
velopment, but hypoxia and anemia together may have compound effects on cerebral oxygen delivery.

Another limitation of using physiologic stability scores is that physiologic instability associated with different disease processes may cause adverse outcomes through different pathways. For example, sepsis was a common finding in the most unstable infants. Sepsis frequently leads to physiologic instability, including hypotension, hypoxia, and hypoxic/ischemic events (all of which were associated with abnormal outcomes in this study). These physiologic derangements could lead to brain ischemia or neural damage by themselves. However, an additional explanation has been offered recently. During episodes of sepsis, tissue necrosis factor and cytokines are often released. The use of physiologic scoring systems alone cannot delineate which abnormal outcomes might be attributable to direct effects of hypoxia, ischemia, or acidosis and which effects might be related indirectly to sepsis through another pathway.

Despite these potential limitations, our study found clear associations between cumulative SNAP scores and mental, motor, and receptive language development through 2 years of age in extremely premature infants. Whether these effects will persist into childhood is unknown. The process of synaptogenesis is merely beginning during the last half of gestation. After birth (at term), there is a rapid burst in cortical synapse formation that lasts through most of the first year. Pruning of synapses (which is thought to be an experience-mediated process) continues for several years. Thus, much of brain development is determined after discharge from the neonatal intensive care unit. With adequate nutrition, physiologic stability, and a positive rearing environment, many of the negative effects associated with physiologic instability might be overcome. Indeed, in this study, the correlation of the SNAP score with developmental indices was not as strong at 2 to 3 years as it was at 1 year adjusted age (Table 5). It is possible that physiologic instability will be less predictive of outcome as the children become older. However, early developmental delays often predict the later development of low intelligence or learning disabilities. It would therefore be useful to determine whether there are any long-term implications of neonatal physiologic instability in terms of either global intelligence or specific cognitive function (such as attention, mathematics, or visual-spatial skills).

Given that neurodevelopmental morbidity remains a constant concern for extremely premature infants, in future studies, it will be important to continue to address the question of how these sequelae evolve from a mechanistic perspective. The SNAP score contains many physiologic factors known to have direct effects on neurons, crossing the boundaries of many specific illnesses, such as respiratory distress syndrome and necrotizing enterocolitis. In this study, the SNAP score proved to be a useful framework to evaluate the effects of neonatal physiologic instability on infant development. The results of the study suggest that recurrent or chronic physiologic abnormalities may be an etiologic link between a large and heterogeneous group of complications of prematurity and subsequent adverse neurodevelopmental outcomes. The clinical implication of these findings is that the prognosis should be guarded for chronically unstable neonates, regardless of the results of head imaging studies.

ACKNOWLEDGMENTS
We thank Drs Mark Mammel, Cathie Gatto, Sixto Guiang, Ellen Bendel-Stenzel, Michael Georgiﬀ, and Douglas Richardson for their critical review of the manuscript.

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*Pediatrics* 1998;102;e35
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