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Diarrhea and Its Effect on Growth

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The predominant etiology of diarrhea in the general population of underdeveloped countries is infection by viruses and bacteria. Studies in rural areas clearly suggest an infectious cause. For example, diarrhea initially affects one individual in the family (index case) and then spreads to other family and community members. Infants and toddlers are affected more frequently than older children, adolescents, and adults. The high prevalence of diarrhea in populations with poor personal hygiene and deficient environmental sanitation also points to an infectious cause and is supported by the identification of rotaviruses, *Campylobacter*, enterotoxigenic enteric bacteria, *Cryptosporidium*, *Shigella*, *Vibrio cholerae*, *Salmonella*, *Giardia*, and other parasites in most patients with diarrhea.

Longitudinal studies of children in deprived ecosystems have documented the significance of diarrheal disease in respect to poor nutrition and growth.[1-3] These studies reveal not only the frequency of diarrhea in infants and young children but also the severity of damage from infectious diseases of the GI tract and their resultant inhibition of good nutrition and normal growth. Many children in Guatemala, Bangladesh, and northeastern Brazil experience from six to nine episodes of diarrhea per year during their first three years of life.[1-3] Most episodes last for a few days and resolve without serious consequences. Other incidents result in considerable losses of fluids and electrolytes or are accompanied by fever, anorexia, and considerable damage to the intestinal mucosa. The worst episodes yield sequelae and permanent damage, such as growth retardation, or result in death.

continued on page 2

Perspectives on Intrauterine Growth Retardation

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Introduction

Fetal growth can be defined in terms of changes in newborn size, organ growth, and maturation, and by the many biochemical adaptations that prepare the fetus for extrauterine existence. Intrauterine growth retardation (IUGR) can result from environmental and genetic influences that limit the intrinsic potential of the fetus to grow, or that restrict growth because of decreases in the amount of available nutrients. IUGR is most commonly defined as a birth weight of less than the tenth percentile at a given gestational age. It is only within the past 20 to 25 years that clear distinctions have been made between low birth weight caused by IUGR and that due to preterm labor. There may be a considerable overlap between IUGR and preterm delivery, which refers to birth at less than 38 weeks' gestation, largely because some of the same risk factors are common to both conditions. Teenage pregnancy, for example, may result in high risk for both prematurity and IUGR. Prognosis of IUGR depends on the underlying condition to a major degree.

Influences on Fetal Growth

A variety of genetic and environmental factors affect fetal growth.[1,2] Genetic factors may be responsible for species or popu-

continued on page 5

In This Issue

Diarrhea and Growth

continued from page 1

Effect of Diarrhea on Growth

Upon detection of growth deficiency or failure to thrive, pediatricians in industrial nations rarely consider infection as the first diagnostic possibility. In these nations, most problems of growth failure due to gastrointestinal disturbances are related to physiologic, enzymatic, immunologic, or metabolic alterations of a noninfectious nature[4] rather than infectious causes.

In developing countries, however, the situation is quite different—particularly in infants who are not breast-fed. Interestingly, most breast-fed children grow very well, even under extreme poverty.[1] By contrast, most children in poor rural and urban areas who are not breast-fed suffer several diarrheal episodes each year, usually resulting in weight loss. Diarrhea-induced weight loss is difficult to correct without prompt and adequate nutritional dietary therapy. Diarrhea often persists in children, even after correction of the infection. This persistence and recurrence of diarrheal episodes generally do not permit catch-up growth. This sequence of events is exemplified by the typical Guatemalan village child whose growth is illustrated in Figure 1.[5] In many rural areas, from 5% to 20% of the diarrheas persist for several days or weeks because of *Shigella* infections. Unfortunately, appropriate antibiotic therapy required for resolution of these infections is not available in most poor rural areas.

Another possible factor in persistent diarrhea is lactose intolerance—a frequent finding, particularly in viral diarrhea during the first year of life. For these infants, diarrhea persists for as long as they are fed cows' milk.

The Guatemalan boy whose growth curve is diagrammed in Figure 1 grew well during the period of exclusive breast-feeding and his growth parameters fell along the 50th percentile of the growth chart of the National Center for Health Statistics (NCHS). When food supplementation was begun at approximately 6 months of age, however, a continuum of diarrheal episodes and weight loss was observed in connection with recurring gastrointestinal and upper respiratory infections. By 1 year of age, the child had experienced several bacterial and viral infections, and altered physical growth was apparent.[6] In addition, infection with parasitical organisms, such as round worms, may also disturb normal growth[6] and may have contributed to alterations in this child.

By age 1, the child was distinctly wasted. The encounter with a variety of viruses, bacteria, and parasites continued, and for one year the child remained wasted and at risk of developing severe protein-energy malnutrition or of dying. The possible metabolic and hormonal disturbances in children under such circumstances—who represent the majority of cases in deprived villages and slums—have not been established.

Field studies show that diarrhea adversely affects nutrition and physical growth.[7-9] Figure 2 illustrates the relationship of growth retardation to diarrheal episodes in two Cauque children. Each recorded episode of diarrhea of known or unknown etiology coincided with an arrest in linear growth. These arrests were of shorter duration and negligible consequence during the first months of exclusive, intensive breast-feeding; upon weaning, however, the magnitude of arrested growth was more marked, often extending for several weeks or months. The effect was even more pronounced in the child with severe fetal growth retardation, as seen in the right side of Figure 2.

These cases demonstrate the prolonged effects of inadequately treated diarrhea and the lack of rapid catch-up growth because the child is repeatedly stricken with infectious episodes. Eventually, the cumulative effects of these episodes (with the additive effects of otitis media, acute respiratory infections, or exanthemas of early childhood) result in a markedly diminished growth rate. In the study village, virtually all children showed some degree of stunting by age 2 years. Cohorts defined by birth weight or by fetal maturity

Figure 1. Typical growth pattern of a Guatemalan village child. Note the drop-off in growth at about five months when the child was weaned from breast milk.

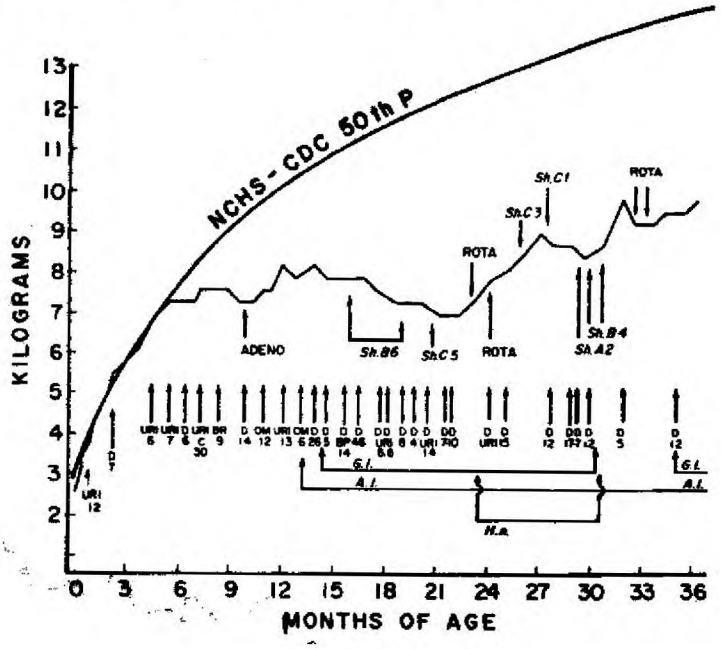
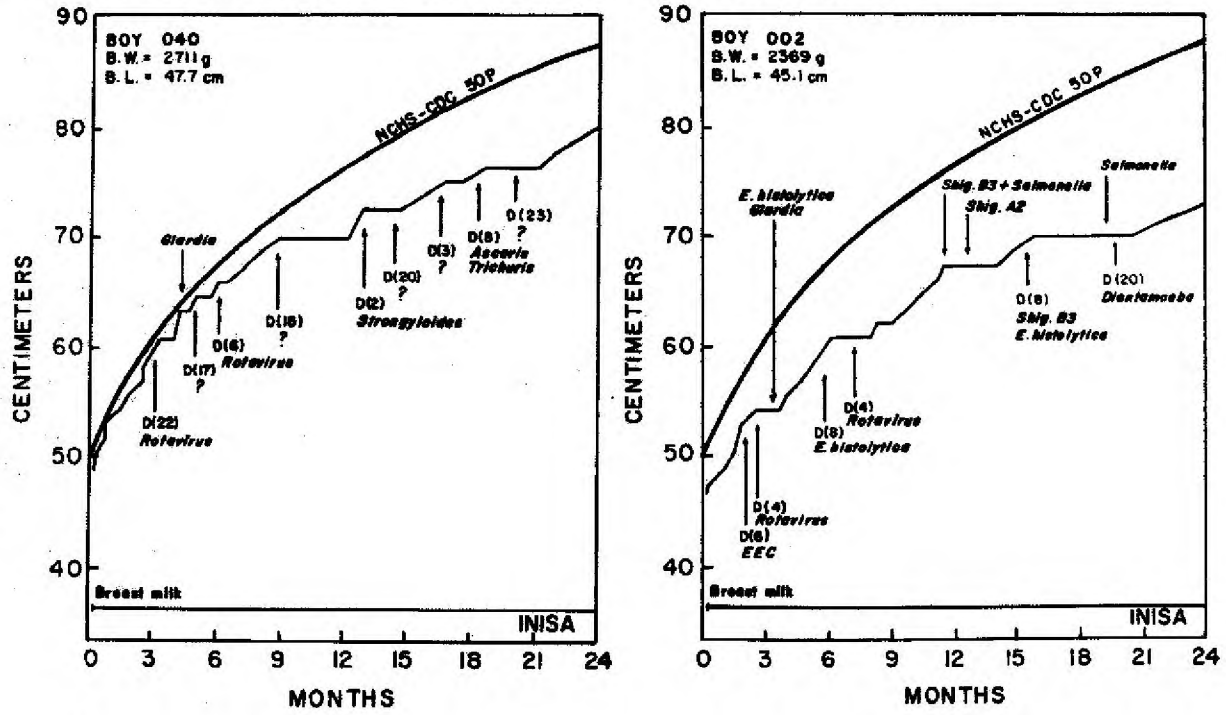


Figure 2. The relationship of drop-offs in growth to infectious diseases is clearly illustrated in these two children. The effect is more pronounced in the pattern on the right of a child with severe fetal retardation.



exhibited a positive correlation between intrauterine growth and poor postnatal physical growth.[1,7] The greatest impact is delivered by the adverse microbial environment of underdeveloped countries.[1,5] Overall growth deficit and much of the wasting reported in children throughout the world is probably the result of repetitive diarrheal diseases and other infections, which severely aggravate an already marginal or poor nutritional intake.

A long-term study, conducted in the poor, rural population of Costa Rica, a country in transition, demonstrated that growth was significantly improved as better sanitation was developed.[9] Although food supplementation during weaning frequently was not improved, the less intense infectious environment resulted in very low rates of enteric infection and diarrheal disease.[10] While growth failure was occasionally observed, it was the exception and was attributable to organic disorders or child neglect, as is the case in industrial nations.[9]

Infectious Diarrhea Induces Malnutrition

Diarrheal diseases are the most important inducers of malnutrition worldwide, because they alter nutrition—and growth—through reduced food intake, disturbed digestion and absorption, impaired use of nutrients, and other metabolic alterations. Each episode has a varying impact on the host economy and nutrition, even when there is no limitation in food availability.[7] Diminished intake of food during diarrheal episodes is often substantial, especially among infants and toddlers. There are two predominant causes: anorexia and restriction dictated by traditions, beliefs, and taboos. In the latter case, the mother or other caretaker suppresses the food intake for days or even weeks, in the belief that food perpetuates the diarrhea.

Anorexia appears to be the most significant reason for decreased food consumption. It is triggered by interleukin 1 (previously known as leukocyte endogenous mediator) and by cachectin (tumor necrosis factor), hormone-like substances released by macrophages and monocytes under the stimulus of infections or other stress. A manifestation of the "generalized acute-phase metabolic response," anorexia occurs regardless of the type, severity, and localization of infection.[11] Most foods are rejected, although breast milk is least so. The intensity of anorexia does not always correlate with the kind or severity of illness, and a child may become anorectic even with a common cold or mild diarrhea. The effect may last a few hours or extend for days or weeks. As much as 20% to 70% of the available food may be wasted or uneaten during bouts of diarrhea.[7]

Microbial action also increases intestinal secretion and lysis of cells in villous tips by rotaviruses, for example, or by stimulation of cyclic AMP and cyclic GMP by bacterial enterotoxins such as *Escherichia coli*. If repetitive losses are not corrected by rehydration and other therapies—

continued on page 4

Diarrhea and Growth

continued from page 3

often unavailable in villages in poor countries—they contribute to malnutrition. Hypersecretion also can be induced by bile and fatty acids, hormones, and neurotransmitters, and by greater calcium cell permeability induced by mediators.[12] Agents such as *Giardia* adhere to the surface of enterocytes, while others such as *Cryptosporidium* lodge under the microcalix but outside the cytoplasm. Some parasites multiply within epithelial cells and in the lamina propria, causing inflammation and bleeding (*Shigella*), or burrow in tissue, eliciting a granulomatous response (*Entamoeba*), or they reach lymph and blood vessels, resulting in sepsis (*Salmonella*).

These infections may generate profuse loss of water, electrolytes, cells, and nutrients, reducing the host to a state of acute malnutrition. Patients, especially infants and young children, may lose 10% or more of their body weight within hours, and may die if shock and dehydration are not promptly corrected. Cells, plasma, amino acids, lipids, vitamins, and hormones may be lost with injury to intestinal mucosa. The dysentery diarrheas are more damaging because they often are accompanied by a protein-losing enteropathy,[13] and exhibit toxic manifestations with weakness and prostration and high mortality.

As with other infections, diarrhea is accompanied by anorexia and fever, breakdown of muscle protein, discharge of insulin and glucagon, mobilization of leukocytes, and sequestration of zinc and iron. Vasoactive intestinal polypeptide (VIP), which inhibits the peristaltic reflex, and other gut hormones (motilin, enteroglucagon, and neurotensin) are increased or decreased during diarrhea. Prostaglandins are increased in diarrhea, including the mild forms seen in toddlers.[14]

Conclusion

Infectious diseases, and diarrhea in particular, are the main determinants of wastage and stunting of growth in children in underdeveloped countries. Nations that are able to diminish the incidence of diarrhea and other infections clearly exhibit a secular change in growth and height of children, as observed in Chile, Costa Rica, and other countries in rapid transition.[5,15,16] Children with no or fewer infections have better appetites, and their healthy parents provide better care. In turn, society benefits because of better use of available resources and increases in production. This might explain, in part, why certain very poor areas, which remain basically poor and consume minimal food, exhibit a remarkably good health condition. One example is the State of Kerala in India.[16]

Equally interesting is the observation that in some undeveloped countries, provision of food supplementation or food distribution centers has been unsuccessful in combating malnutrition. In particular, this is especially noticeable in the continuing presence of poor sanitation, which leads to diarrhea and other infectious diseases. As part of any major policy to prevent malnutrition in underdeveloped countries, attention must be directed toward the control of infectious diarrhea. Only in this way can malnutrition and growth failure be prevented.[5,17]

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Perspectives on Intrauterine Growth Retardation

continued from page 1

lation differences in size at birth. Mean birth weight in human populations can range from 2,400 g in New Guinea to 3,880 g in American Indian populations. Although some of these differences can be explained by factors such as nutrition and maternal size, it is likely that ethnic differences in birth weight occur regardless of socioeconomic status. Males weigh an average of 150 to 200 g more than females at birth. This difference occurs in late gestation and may be related to the testosterone produced by the male gonad, but this has not been proven.

Hormones are important for fetal maturation and for many of the adaptive events that prepare the fetus for extrauterine existence. Insulin appears to be the principal growth hormone for the fetus. Other classic hormones appear to influence specific organ development rather than fetal size. For example, testosterone induces virilization of the genitalia, glucocorticoid influences lung maturation, and thyroxine modulates central nervous system development. With the exception of somatomedins, other putative growth factors, including epidermal growth factor, nerve growth factor, and transforming growth factors, are of likely importance in regulating organ growth and differentiation without greatly influencing newborn size. Somatomedins are present in and synthesized by a variety of fetal tissues, and umbilical cord levels of somatomedin-C have been correlated with birth weight.

Genetic and/or chromosomal disorders can profoundly alter fetal growth, with the degree of growth failure reflecting the specific defect. Growth retardation is a major feature of Down's syndrome, trisomies 13 and 18, and Turner's syndrome. Intrauterine infections may be responsible for as many as 10% of cases of IUGR and should always be considered in the evaluation. IUGR is commonly seen as part of the symptom complex caused by toxoplasmosis, congenital syphilis, rubella, cytomegalovirus, and herpes simplex (the TORCH organisms). Recently, IUGR-associated malformations, including microcephaly and craniofacial abnormalities, have been described in newborns with an AIDS-related embryopathy.[3]

Drugs and chemicals causing IUGR include classic teratogens, such as antimetabolites, as well as common therapeutic agents such as phenytoin, trimethadione, and warfarin. Heroin addiction, cigarette smoking, and heavy alcohol use are also commonly associated with IUGR. More than 50% of infants born to mothers who drink heavily will be abnormal. In one study, the incidence of IUGR was 7% in babies whose mothers were light-to-moderate drinkers and 27% in those whose mothers were heavy drinkers.[4] Cigarette smoking is a powerful determinant of IUGR and results in a birth weight deficiency of 150 to 250 g.[5] This is most likely related to the combined effects of smoking on maternal appetite, uteroplacental blood flow, and maternal blood levels of carbon monoxide that further impair oxygen delivery to the fetus.

The terms "proportionate" and "disproportionate" have been used to distinguish IUGR newborns with decreased growth potential from those with restricted growth due to impairment of maternal nutrient delivery. Fetuses and newborns with decreased nutrient supplies exhibit disproportionate growth because of a relative sparing of brain growth, whereas congenital infections or genetic diseases that restrict growth potential result in proportionate or symmetrical growth retardation. These patterns of growth can be detected in utero and may indicate the underlying condition that ultimately results in IUGR. Poor maternal weight gain and fundal growth should alert the obstetrician to the likelihood of IUGR so that ultrasonography can be utilized to follow fetal growth parameters such as the biparietal diameter or the relationship of the head size to the body size (which can be used to identify proportionate or disproportionate fetal growth in utero).

Fetal Malnutrition

Fetal malnutrition is the most common cause of low birth weight. It can result from maternal malnutrition or from failure of the fetal circulation to deliver adequate substrates to the fetus generally because of maternal diseases that restrict uteroplacental blood flow. Conditions resulting in decreased uteroplacental blood flow include toxemia of pregnancy and maternal hypertension secondary to chronic renal disease. Fetuses in multiple pregnancies may exhibit restricted growth because of failure of the uteroplacental unit to provide optimal nutrition to more than one fetus in the uterus. The smaller twin of a monozygotic pair frequently exhibits IUGR because of arteriovenous communications within the chorionic plate that can severely compromise blood flow to one twin. IUGR is also observed in infants born in high-altitude regions and in those born to mothers with cyanotic congenital heart disease, presumably because less oxygen is available in both instances.

Maternal Regulation of Growth

Walton and Hammond[6] reported that foals of Shire horses bred with Shetland ponies reflected the size of the mother. Shetland/Shire crosses born to a Shire mare were the size of normal Shire foals, whereas the foals born to the Shetland dam and the Shire cross were the size of the normal Shetland foal. Similar data in other species, including humans, suggest that constraints on fetal growth are imposed by the maternal uterine environment. In human pregnancies, fetal growth is generally not affected by the number of fetuses prior to the 26th week of gestation. After 27 weeks of gestation, however, the growth rate is slowed for triplets; the rate slows after 30 weeks for twins. Uteroplacental constraints may even become op-

continued on page 6

continued from page 5

erative in singleton pregnancies when a weight of about 3,000 g is achieved regardless of the number of fetuses.

The Dutch famine of 1944-45 resulted in a mean birth weight reduction of about 300 g.[7] This effect was observed primarily when the period of starvation occurred within the last trimester of pregnancy. Behavioral testing and IQ performance data did not reveal any deficiencies when the population at risk was studied more than 20 years later.

IUGR caused by malnutrition may be multigenerational. In a marginally nourished rat colony maintained over nine generations, maternal weights and newborn sizes were markedly reduced when compared with those in normally nourished controls.[8] With reinstitution of normal nutrition after five generations of marginal nutrition, it appeared that more than one generation of good feeding was necessary to correct the deficits.

Clinical Evaluation of IUGR

Evaluation of the newborn with IUGR begins with measuring length, weight, and head circumference and plotting the results on standard growth charts to determine if the pattern of growth is disproportionate or proportionate. The Lubchenco charts are most commonly used although they may underestimate IUGR as compared with other standards. A careful assessment of gestational age should be made for all infants. Accurate dates can be confirmed by ultrasound examination of the fetus in early pregnancy or estimated less precisely by the Dubowitz exam immediately after birth.

Infants with nutritional IUGR have a scrawny, wasted appearance because they have so little subcutaneous fat. Many of their problems are associated with decreased metabolic reserves. These infants are at increased risk for asphyxia and meconium aspiration; therefore, when IUGR is detected antenatally, there should be appropriate monitoring and careful planning concerning the mode of delivery.

Newborns with IUGR are also at increased risk for hypoglycemia and polycythemia. Hypoglycemia is probably due to low fuel reserves and a decreased capacity to carry out gluconeogenesis. Polycythemia occurs in response to the increased erythropoietin levels secondary to relative intrauterine hypoxia. Chronic intrauterine hypoxia may also result in persistent pulmonary hypertension with marked right-to-left shunting because of abnormal thickening of the small pulmonary arterioles in the hypoxic fetus. These are primarily problems of the nutritionally growth-retarded newborn. Those with IUGR secondary to congenital infection and/or genetic disorders are less likely to develop these complications.

Fetal Adaptation in IUGR

While serious pathology may clearly be the consequence of markedly reduced uteroplacental blood flow, the majority of infants with nutritionally based IUGR have normal development and do not show significant differences in IQ or neurological scores when compared with normal newborns.[9] A strong case can be made that many of the features of nutritional IUGR represent fetal adaptation to a restricted nutrient environment rather than a pathologic condition.[10] Those fetuses with sufficient time to adapt to compromised nutrition may maximize their prospects for a favorable outcome.

In such infants, brain growth is spared because of a redistribution of fetal blood flow. A smaller overall fetal size may reduce substrate and oxygen needs to what can be provided by an impaired uteroplacental circulation. A redistribution of blood flow to the head supports brain growth and head circumference at the expense of both weight and linear growth. Increased blood flow to the brain associated with decreased blood flow to the viscera increases the ratio of head circumference to abdominal circumference; this ratio can be measured in utero with ultrasound and thus identifies disproportionate IUGR antenatally. Vasopressin released in response to oxygen and/or nutrient deficiency is a likely mediator of increased blood flow to the brain. Polycythemia exhibited by these infants can also be viewed as an adaptation that results in an increase in the capacity of the blood to carry oxygen to the organs and tissues of the growth-restricted fetus.

Finally, severe nutrient restriction appears to be associated with accelerated maturation. Data from experimental animals and in humans suggest a lower incidence of hyaline membrane disease in fetuses with IUGR, which may increase survival if the fetus with IUGR is born prematurely. The infant with IUGR may therefore represent a successful adaptation to a substrate-deficient intrauterine environment. Those infants with IUGR who have sufficient time to adapt to a substrate-deficient intrauterine environment may be at lower risk for serious hypoxic injury that may occur in large fetuses born at term but subjected to acute uteroplacental compromise at the time of delivery. In other words, smaller may be better.

If maternal constraints on fetal growth can be viewed as an adaptation in the IUGR pregnancy, questions can be raised about the effects of intervention programs designed to increase fetal weights. This may potentially cause an adverse outcome in chronically malnourished populations that have already adapted to malnutrition and a constrained uterine environment. Careful evaluation and follow-up of such intervention programs are necessary.

In summary, adverse genetic and environmental influences can impose severe constraints on growth. IUGR resulting from congenital infection, genetic or chromosomal defects, and/or drugs and other environmental insults is likely to be associated with long-

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term developmental disability. Fetuses with IUGR secondary to intrauterine nutritional deprivation may have more favorable outcomes due in large part to adaptations such as decreased fetal size with sparing of brain growth, mild polycythemia, and enhancement of pulmonary maturation. In many such infants, IUGR is an advantageous adaptation rather than a pathologic condition.

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IN FUTURE ISSUES

The Concepts and Mechanisms of Genetic Linkage
by Thaddeus Kelly, M.D.

Genetic Linkage and Endocrine Disease
by Thaddeus Kelly, M.D.

Turner's Syndrome
by Judith G. Hall, M.D.

Directory of Resource Groups for Patients with Endocrine and Genetic Disorders

Letter to the Editor

Russell-Silver Syndrome

In Vol. 2, No. 2 of *Growth, Genetics, and Hormones*, an article by Saal et al entitled "Reevaluation of Russell-Silver Syndrome" was abstracted. The Editor's Comment on that abstract prompts this letter.

One of the reasons that the Russell-Silver syndrome is heterogeneous is that *there is no such thing as the Russell-Silver syndrome*. Dr. Russell and Dr. Silver, in their original reports, described two entirely different syndromes. It is a mistake to combine the two and perpetuate the combination. I have mentioned this to Dr. Alex Russell, who agrees. Dr. Silver even described increased urinary gonadotropins in his patients. I point this out to our house staff when they refer such a patient to our clinic. In my experience, most of the patients referred to me for dwarfism, triangular facies, and intrauterine growth retardation fall into the "Russell" category. I have yet to see a patient with increased gonadotropins at a young age in the hemihypertrophy syndrome described by Silver. I continue to be a splitter instead of a lumper.

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Dr. Blizzard's Comments

Dr. Green's letter is in accord with the article written by Saal et al and published in the *Journal of Pediatrics* 1985;107:733. These authors stated that the Russell-Silver syndrome is a heterogeneous entity. Dr. Green would say it is not an entity at all. Undoubtedly, many would agree with Dr. Green. I have asked Dr. Silver to respond and his comments are listed below.

Dr. Silver's Comments

The confusion about the Silver-Russell syndrome will undoubtedly continue until the specific etiology(s) of the syndrome has (have) been defined and/or a specific diagnostic laboratory test is available. Although the heterogeneity of findings suggests that multiple etiologies may be involved, there is no concrete evidence that this is so.

The Silver-Russell syndrome certainly fits the definition of a syndrome: "the sum of signs of any morbid state; a set of symptoms occurring together" (Dorland). As with most other syndromes, not every child with the Silver-Russell syndrome has every finding. However, the combination of all or most of the findings of congenital short stature continuing into childhood, asymmetry involving various parts of the body, triangular facies, clinodactyly, cafe-au-lait areas of the skin, syndactyly of the toes, and elevated gonadotropins (as first described by me in 1953, and in subsequent publications, and by Russell in 1954) occurs with sufficient frequency to be considered a specific syndrome with one or more etiologies.

Originally, the syndrome was known as the Silver syndrome in this country and the Russell syndrome in Europe. More recently, it has been termed the Silver-Russell syndrome or the Russell-Silver syndrome. Hopefully, Drs. Green, Saal, and others will soon provide us with the information that will permit us to make etiology-based diagnoses. Until then, I believe it is reasonable to continue using the names that have historically been assigned to what appears to be a single clinical syndrome with a characteristic phenotype.

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The address given for the Prader-Willi Syndrome Association in Volume 2, Number 3 was in error. The correct address is: 5515 Malibu Drive, Edina, Minnesota 55436. The phone number is 612-933-0113. Marge A. Wett is the Executive Director.

Short Stature in Anorexia Nervosa Patients

In following 104 patients with anorexia nervosa, the authors found 85 suitable for comparison with 85 age-matched controls. As seen in the Table, a large percentage of the anorexic patients were short.

Information was available regarding parental heights for 35 patients. The mean actual height was at the 34th percentile, compared to a mean expected height at the 48th percentile, based on calculations of parental heights. Twenty-six females were postmenarchal, permitting comparison with the adjusted mid-parental height (Tanner scale). Nine had evidence of growth impairment and could not be classified under "familial short stature" by this method.

The patients' age at onset of anorexia ranged between 10 and 22 years. Symptoms first appeared an average of 12.9 months before seeking therapy, and the mean weight loss was 29 pounds (25% of total body weight). Of great importance in considering the etiology of the short stature is the fact that 80% developed anorexia after menarche, with symptoms of onset occurring more than one year postmenarche in 61%.

Table Height-Related Statistics in Study Participants

	Anorexic patients		Controls		
Height percentiles	n	%	n	%	Expected, %
<5	12	14	1	1	4
5-9	3	4	4	5	5
10-24	28	33	16	19	15
24-49	22	26	28	33	25
>50	20	23	36	42	50

The conclusion is that some factor(s) other than malnutrition may account for the fairly high incidence of short stature. Possibly, there is a pathophysiologic factor producing short stature and, subsequently, anorexia. Patients with anorexia sometimes exhibit several indications of a hypothalamic abnormality affecting thyroid, gonadal, and adrenal function. The authors state that excessive somatostatin production cannot be excluded.

Nussbaum M, Baird D, Sonnenblick M, et al. *J Adolesc Health Care* 1985;6:453-455.

Editor's comment—*These data are not only important but also provocative, since they are unexplained within the context of current knowledge. Most patients with anorexia might be expected to have growth failure secondary to malnutrition. In the majority of these patients, growth retardation preceded malnutrition. Growth hormone levels are increased in most patients with anorexia, although IGF-I values are low, as is expected with starvation. We do not know whether GH and IGF-I levels are normal before the onset of anorexia. If available, these data might provide insight regarding the etiology of anorexia nervosa.*

Furthermore, could these patients have hypercortisolism long before the anorexia begins? (See the review of the endocrine symposium on neuropsychiatric disorders, reported by Dr. Lifshitz in this issue.) If present, hypercortisolism could account for the growth retardation.

Hypercalciuria, Hyperphosphaturia, and Growth Retardation in Children With Diabetes Mellitus

The authors evaluated 157 diabetic children, 6 to 16 years of age, with insulin-dependent diabetes mellitus (IDDM) from 0.2 to 14 years. Eleven percent of the 157 subjects were shorter than would be anticipated, as assessed by comparison with the controls. Increments in height became smaller with the duration of IDDM and differed significantly from controls when IDDM had been present for more than seven years.

Growth retardation correlated with increased calcium and phosphorus excretion (as reflected by increased Ca/Cr and P/Cr ratios) and with poor control of IDDM (as evidenced by glycosylated hemoglobin assays). Hypercalciuria was *not* correlated with increased serum calcium or other evidence of bone calcium mobilization. Hypercalciuria is reportedly caused by hypophosphatemia, and there was an inverse relationship between serum phosphorus and an increase of urinary P/Cr and Ca/Cr. Renal disease could not be demonstrated as a cause of increased Ca and P excretion when it occurred. The urinary loss of Ca also correlated inversely with plasma glucose at the time of urine collection. The increased urinary phosphorus appears to result from competition between glucose and both Ca and P for renal tubular reabsorption. There was some evidence of hypercalciuria as a renal response to functional phosphorus deficiency.

The authors conclude that the higher incidence of short children with IDDM is primarily associated with poor metabolic control, but the specific mechanism(s) of impaired growth is (are) not well defined and may not be due to a single cause.

Malone JI, Lowitt S, Duncan JA, et al. *Pediatrics* 1986;78:298.

Editor's comment—*This study is very well done and carefully analyzed. The authors speculate that phosphorus supplementation might be beneficial. Further studies are certainly indicated to elucidate the causes and results of hypercalciuria and hyperphosphaturia, which are frequently seen in patients with poorly controlled IDDM. (See Harrison's article in* Growth, Genetics, and Hormones, *vol. 2, no. 2.)*

First Trimester Prenatal Diagnosis: Three Reports

Prenatal diagnosis of severe congenital diseases and malformations, which permits selective termination or altered management of affected pregnancies, has become an accepted part of modern medical practice. In the 1970s, amniocentesis and real-time ultrasound evaluation of the fetus during the second trimester were introduced for prenatal diagnosis. In the early 1980s, first trimester sampling of the chorionic villus (the fetal part of the placenta) was developed as an alternative modality for prenatal diagnosis. By the end of 1985, sampling procedures of more than 1,000 chorionic villi had been performed for prenatal diagnosis during the first trimester in ongoing pregnancies.

The article by Jackson in *Seminars in Perinatology*[1] reviews the technique and the indications for first trimester chorionic villus sampling. The technique involves localization of the placenta with ultrasound, and the vaginal removal (by suction under ultrasonic supervision). The test is most easily and safely done between the beginning of the 9th week and the end of the 11th week of gestation. Chromosomal, DNA, and most biochemical assays can be done on chorionic villus material, and the results of such testing are usually available within the first trimester.

The safety and accuracy of chorionic villus sampling have been established by the Internal Chorionic Villus Sampling (CVS) Registry, which was established by Jackson et al two years ago.[2] It is now clear from these data that the incidence of significant complications after CVS is less than 5%. In institutions with experience in the technique, the miscarriage rate after CVS is between 2% and 4%. The background spontaneous abortion rate is approximately 2% or 3%. Thus, additional risk of CVS-caused miscarriage seems small and is probably in the range of 1%. Separation of fetal from maternal tissue is extremely important for accurate CVS results. One complication that has been observed is a higher rate of chromosomal mosaicism in chorionic tissue than in amniotic tissue.

Transabdominal CVS has recently been described by Smidt-Jensen et al.[3] It may be that this technique will avoid or minimize occurrence of infection, which has occasionally been seen in vaginal sampling.

1. Jackson L. *Semin Perinatol* 1985;9(3):209-218.
2. Jackson LG, Wapner RA, Barr MA. *Lancet* 1986;i:674-675.
3. Smidt-Jensen S, Hahnemann N, Hariri J, et al. *Prenat Diagn* 1986; 6:125-132.

Editor's comment—*There are several advantages to first trimester prenatal diagnosis. These include safety for the mother if termination of pregnancy is deemed necessary and a chance to confirm results by second trimester amniocentesis, if appropriate. Earlier testing is also easier to handle psychologically for most families.*

Since prenatal diagnosis is available and since it can be applied to detect many types of growth problems, physicians should be aware of these new advances and the availability of first trimester diagnostic techniques.

Influences in Child Growth Associated With Poverty in the 1970s: An Examination of Hanes I and Hanes II, Cross-Sectional U.S. National Surveys

The association between poverty and growth deficits in children has been reported in developing countries as well as in the United States. In this study, a sample population of 13,750 black and white children aged 1 to 17 years was taken from the Health and Nutrition Examination Surveys, HANES I (1971-1975) and HANES II (1976-1980). These were employed to examine the associations between height, weight, triceps skinfold thickness, subscapular skinfold thickness, and dietary intake measures. The poverty index ratio (PIR) was used to define the poverty threshold. This index represents a more specific measure of poverty than income by including family size and composition, sex of head of household, farm/nonfarm residence, and the current Consumer Price Index. The PIR is widely used by the U.S. Government.

Overall, children above the poverty threshold were taller, heavier, and fatter than children in families living below the poverty level. Specifically, on the average, poor children were 1.3 to 1.9 cm shorter, 2% to 3% lighter in weight, and 3% to 8% leaner (by skinfold measurements) than children above the poverty level. An interesting finding was that there were no reported differences in energy consumption and macronutrient intakes between the two groups. However, a trend toward improved growth among the poor children was noted between the time of the HANES I (1971-1975) and HANES II (1976-1980) surveys.

Jones DY, Nesheim MC, Habicht JP. *Am J Clin Nutr* 1985;32: 714-724.

Editor's comment—*This study suggests that caloric intake does not appear to play a role in the growth failure reported among poor children. Both groups of children consumed equal diets, yet children who were below the poverty threshold were smaller in both weight and height, and had less reserve fat as measured by skinfold thickness than children above the poverty threshold. Other factors that may be associated with poverty, such as more frequent infections, insufficient medical care, and poor sanitation, may have had a negative influence on the growth of the children below the poverty threshold. The authors, however, do not discuss these concerns as they relate to growth.*

Special Report: The Endocrine Society Symposium on Endocrinology of Neuropsychiatric Disorders—June 25-27, 1986, Anaheim, California

Fima Lifshitz, M.D.
Associate Editor—Growth, Genetics, and Hormones

The symposium dealt primarily with the interrelationship of nutrition, neuropsychiatric disorders, and endocrinology. Dr. John E. Morley of the University of California at Los Angeles pointed out that many peptide hormones are involved in the control of human eating behavior. For example, cholecystokinin-8 has been called a satiety factor because of its ability to decrease feeding and delay gastric emptying through vagal activity. Dr. Morley also noted that glucagons, somatostatin, bombesin, calcitonin, naloxone, and other opioid antagonists act centrally as satiety factors. Corticotropin-releasing factor is also a potent anorectic agent. Peptides that enhance feeding behavior include the endogenous opioids, pancreatic polypeptide, galinin, growth-hormone-releasing hormone, and neuropeptide Y (bulimin).

Dr. Michelle P. Warren of St. Luke's-Roosevelt Hospital, New York City, discussed endocrine changes associated with anorexia nervosa. Dr. Warren stated that the incidence of anorexia nervosa appears to be increasing. It afflicts between 0.5% and 1.0% of white adolescents who are in the mid-socioeconomic group. There is a 6% concordance in incidence among monozygotic twins although the reasons for this are poorly understood. The peak age of onset is at about 12 to 13 years of age. For some unexplained reason, anorexia occurs more often in girls with scoliosis. The disorder is very rare among blacks and among men (the male-female ratio is 1:9). However, anorexia nervosa occurs in males who are training for competitive athletic activities and are restricting their food intake. Between 5% and 20% of professional ballet dancers can be classified as patients with anorexia nervosa.

The endocrine changes seen in anorexia nervosa appear to be adaptive phenomena and are similar to those seen in starvation. These include lower levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) and decreased pulsatility of LH over a 24-hour period. The pulsatility pattern reverts to that seen in prepubertal subjects. There is also increased secretion of endogenous opioids, but administration of naloxone restores normal LH secretion in only a small number of patients. Thyroid function resembles that in the "euthyroid sick syndrome," with increased 3:3′, 5′ triiodothyronine concentrations and decreased 3, 5, 3′ triiodothyronine secretion. This reduces the metabolic rate and decreases muscle catabolism. Hypercortisolism often occurs because of

Special Report: National Foundation-March of Dimes Clinical Genetics Conference on Muscle and Its Disorders—June 8-11, 1986, Philadelphia

Judith G. Hall, M.D.
Associate Editor—Growth, Genetics, and Hormones

The National Foundation-March of Dimes has reinstituted the clinical genetics conferences that were so successful in the 1960s and 1970s. The earlier conferences focused on the delineation of birth defects. However, because of advances in molecular genetics, developmental genetics, and clinical genetics, a new format became desirable. The new March of Dimes clinical genetics conferences are aimed at providing a better understanding of a particular organ system. At this year's conference, the subject was muscle. Clinical and basic research dealing with normal and abnormal muscle differentiation, muscle biochemistry, and muscle function was presented, allowing clinicians and researchers to learn from each other's work.

Sir Andrew Huxley convened the conference with a historical overview of muscle disorders. Several presentations on molecular research related to the actin and myosin genes followed. Not only have these genes been mapped and their differences described, but the progressive switching on and off during development and in different tissues is becoming well defined. The mapping of specific genes that are tightly regulated during embryologic and fetal development was clearly outlined at the meeting. Much of this work has been done in culture of muscle cells, but there seemed to be correlations in different animal model systems and in muscle from various sites of the body.

The clinical aspects of well-defined muscle disease, both dystrophies and metabolic disorders, were reviewed. However, a whole new set of specific disorders, many of which can now be understood on a molecular level, were reported by various investigators. Various aspects of myogenesis—both in normal and abnormal cells, and during development and in regeneration—were discussed, as were the interaction of nerve and muscle and the biochemistry related to those interactions.

Experiments of nature—in which individuals with muscular dystrophy have also been growth-hormone-deficient or have had denervation, as by polio, but have not developed the usual muscle deterioration—indicate that many environmental factors can affect genetically determined muscle

decreased clearance of free cortisol, and it is presumed that there is increased secretion of corticotropin-releasing factor (CRF). Growth hormone is increased, but somatomedin-C (IGF-I) levels are decreased; this may conserve nitrogen. There is increased sensitivity to insulin, and norepinephrine secretion is reduced. Vasopressin also appears to be reduced and this may cause difficulty in handling water loads.

Consequences of the amenorrhea induced by starvation may be osteoporosis, stress fractures, and aseptic hip necrosis. All of these conditions are much more common in patients with anorexia than in normal females. Osteoporosis may result from scoliosis, but scoliosis may actually precede anorexia, an interesting observation.

Dr. George F. Koob of the Scripps Clinic and Research Foundation in La Jolla, California, discussed behavioral and endocrine effects of CRF on the central nervous system (CNS). CRF is a potent stimulus for both adrenocorticotropic hormone (ACTH) and beta-endorphin release. It has also been shown to increase CNS activity in a manner much like that of caffeine, and it potentiates the acoustic startle response. CRF also affects the limbic system, with its primary effects on learning and behavioral pathology, aggression, and changes in sexual behavior.

Another presentation at the symposium dealt with the pathophysiology of hypothalamic-pituitary-adrenal dysfunction in depression and anorexia nervosa. Dr. Philip W. Gold of the National Institute of Mental Health of the National Institutes of Health in Bethesda, Maryland, reported that hypothalamic dysfunction has been shown to be present in anorexia nervosa and depression. Moreover, the hypercortisolism present in both disorders appears similar in pathophysiology, but different from that observed in Cushing's disease. Dr. Gold stated that in both depression and anorexia nervosa, there is probable increased secretion of endogenous CRF, attenuated ACTH responses to CRF, and adrenal hyperresponsiveness to ACTH. These abnormalities resolve when the patients gain weight. The hypercortisolism in depression and anorexia nervosa represents a central defect, whereas the hypercortisolism of Cushing's disease is believed to be caused by a defect of excessive ACTH secretion that seems to be localized in the pituitary. Dr. Gold and his co-workers believe that endogenous CRF secretion in patients with depression and anorexia nervosa may be significant in the symptom complexes of these illnesses.

function and deterioration. It appears that the size of muscle cells in Duchenne's muscular dystrophy may be critical in the dystrophic process. Growth hormone deficiency can slow the rate of progression of muscular dystrophy, possibly by limiting the size of the muscle cell. This and other observations give hope that new approaches to symptomatic therapy can be found. Fortunately, new techniques for studying muscle size, composition, and function, such as nuclear magnetic resonance, are beginning to yield clues about normal muscle physiology at the molecular level and about the distribution of abnormalities within the muscle cells.

Many well-known syndromes in which the etiology has not been defined—such as Marfan, Schwartz-Jampel, and Marinesco-Sjögren syndromes—were examined as possible muscular dystrophies.

Perhaps the most exciting recent advance has been the molecular analysis of the Duchenne's muscular dystrophy gene locus. Two approaches have been used: that of "walking" along the X chromosome and the use of DNA from girls with Duchenne's muscular dystrophy who have X-autosome translocations that can be studied on a molecular level. The area of the Duchenne gene is now starting to be "peppered" with probes that allow prenatal diagnosis and carrier detection. It is now considered likely that the gene locus for Becker's muscular dystrophy is either within or very close to that for Duchenne's muscular dystrophy. Linkage analysis of other myopathies and muscle problems is improving as well. For example, the linkage of myotonic dystrophy, by using more closely linked genes, now enables much more accurate prenatal diagnosis and premorbid recognition.

In general, the conference was exciting and stimulating, because it encouraged interaction between basic research scientists and clinicians. It is exciting to see how much progress has been made in an area in which new findings and techniques can be rapidly applied to clinical conditions. We look forward to seeing this same approach being used in future March of Dimes conferences to elucidate other organ systems. In this way, birth defects and genetic diseases will be further delineated.

MEETING CALENDAR

January 25-28 34th Postgraduate Course, American Diabetes Association. Marriott's Orlando, Florida. Contact: American Diabetes Association, 1660 Duke Street, Alexandria, VA 22320 (800-232-3472)

March 15-24 International Postgraduate Course in Endocrinology. Siena and Assisi, Italy. Contact: Loretta Giacoletto, Washington University School of Medicine, P.O. Box 8063, 600 South Euclid Street, St. Louis, MO 63110 (800-352-9862)

March 23-27 14th Training Course on Hormonal Assay Techniques. Bethesda, Maryland. Contact: Nettie Karpin, Executive Director, The Endocrine Society, 9650 Rockville Pike, Bethesda, MD 28014 (301-530-9660)

April 27-30 Annual Meeting of the American Pediatric Society/Society for Pediatric Research. Disneyland Hotel, Anaheim, California. Contact: Debbie Wogenrich, Department of Pediatrics, University of New Mexico, Albuquerque, NM 87131 (505-277-6628)

May 1 Annual Scientific Session, Lawson Wilkins Pediatric Endocrine Society. Disneyland Hotel, Anaheim, California. Contact: Dr. Gilbert August, Department of Endocrinology and Metabolism, Children's Hospital, 111 Michigan Avenue NW, Washington, DC 20010 (202-745-2121)

May 8-14 Spring Session, American Academy of Pediatrics. Ramada Renaissance, San Francisco, California. Contact: Neal Baker, Department of Education, American Academy of Pediatrics, P.O. Box 927, Elk Grove Village, IL 60007 (800-433-9016)

June 4-12 47th Annual Meeting and Scientific Sessions, American Diabetes Association. Hyatt Regency Hotel, Indianapolis, Indiana. Contact: American Diabetes Association, 1660 Duke Street, Alexandria, VA 22320 (800-232-3472)

June 10-12 69th Annual Meeting, The Endocrine Society. Indianapolis Convention Center, Indianapolis, Indiana. Contact: Nettie Karpin, Executive Director, The Endocrine Society, 9650 Rockville Pike, Bethesda, MD 20814 (301-530-9660)

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