

gestation proceeded and was significantly higher for mutant compared to normal pregnancies reflecting the small placenta size.

To address the discrepancy between placental and fetal growth, the authors compared normal and mutant placentas structurally and functionally. Other than size, no obvious differences in tissue organization or cell morphology were detected. They next compared maternal-fetal transport of different radiolabelled compounds, one transferred by passive diffusion and the other by active transport. Their results showed that passive diffusion declines proportionate to the relative reduction in placental size. Active or system A transport, however, increases during mid gestation, apparently compensating for the loss of passive transfer until near the end of gestation when this compensation is insufficient to meet the needs of the fetus and fetal growth drops off. Importantly, the system A transporter has been shown to be a determinant of fetal growth.

In summary, deletion of a placental-specific imprinted transcript results in fetal growth restriction, primarily through a decrease in total nutrient transfer across the placenta. This example of a morphologically normal but small placenta affecting fetal growth supports the genetic conflict theory of imprinting, in which a placental-specific gene expressed from the paternal allele regulates the supply of nutritional resources to the fetus. On the other hand, fetal demand for nutrients is genetically regulated by the level of growth factors such as IGF-I and IGF-II. Increasing fetal size therefore requires a higher level of demand (for example, higher fetal IGF-II) as well as a higher level of supply (by increasing, for example, placental surface area). Reduced fetal size can be the outcome of reduced supply (as in the P0 mutant described here) or of reduced demand (for example *Igf1* knockout, which reduces fetal but not placental size). The mouse *Igf2* gene is remarkable in combining the

control of both the supply and the genetic demand for maternal nutrients in a single gene.

Constância M, et al. *Nature* 2002;417:945-948.

First Editor's Comment: *This work supports the genetic conflict theory of imprinting showing that placental-specific genes expressed from the paternal allele contribute substantially to the supply of nutrients a fetus receives from its mother. It also shows that the placenta can partially compensate at least for the loss of this paternal effect. It will be interesting to learn more about the nature of the compensation, which represents a potential mechanism to exploit in treating intrauterine growth retardation. It is important to acknowledge, that the relationship between mother and fetus differs substantially between mice and humans, especially with regard to size and duration.*

William A. Horton, MD

Second Editor's Comment: *As a pediatric endocrinologist who has had a special interest in IUGR for many years, I found the reading of the original article most informative. Not mentioned in the abstract or First Editorial comment was the following brief statement, "At birth, P0 mutant pups were 69% of normal birth weight. This was followed by postnatal catch-up growth which was complete by three months of age." While, as Dr. Horton stated above that mice and humans (may) differ substantially, there is a corollary between the catch up growth in these IUGR mice and the catch up growth that is seen in most IUGR human neonates (primarily those without associated dysmorphology) in the first two years of life. Subsequent studies dealing with the genetic conflict theory in humans should be very informative and intriguing.*

Robert M. Blizzard, MD

Insulin-like Growth Factor I and Leptin in Umbilical Cord Plasma and Infant Birth Size at Term

Umbilical cord blood samples were collected from 12,804 consecutive deliveries, and cord plasma samples were collected from 585 singleton infants born in Norway at term after uncomplicated pregnancies. These were analyzed for plasma leptin, IGF-I, IGFBP-1 and IGFBP-3. Data were analyzed following log transformation of IGFBP-1 and leptin values. Linear regression analysis was used to determine the contribution of maternal and infant factors to umbilical levels of these hormones. The mean age of the mothers of these infants was 28 years. Seven percent had smoked at the beginning of the pregnancy, and 36 percent were primiparous. Male

infants had a higher birth weight and length than girls, but girls had a higher ponderal index. Leptin and IGF-I levels were higher in the cord blood of female infants than in males. None of the maternal factors which were analyzed, including pre-pregnancy weights, smoking, or number of previous pregnancies were significantly associated with levels of cord leptin. IGF-I, IGFBP-3, and leptin increased proportionately with increasing birth weight. Levels of IGF-I and leptin were the strongest predictors of both birth weight and birth length, and were independent of length of gestation, maternal age, parity, pre-pregnancy weight, smoking and offspring sex.

The authors conclude that their data suggest that the sexual dimorphism in the regulation of leptin and IGF concentrations, which previously was demonstrated in later childhood, may already be established at birth. They also suggest a possible role for leptin and/or the IGF-I system in relation to birth size and to the risk of diseases such as non-insulin dependent diabetes and cardiovascular disease which have been shown to be frequent in low birth weight infants.

Vatten LJ, et al. *Pediatrics* 109:1131-1135.

Editor's Comment: *These findings have important implications for understanding the relationship between low birth weight and adult morbidity - especially*

cardiovascular disease, hypertension, and type 2 diabetes. It would appear that leptin, IGF-I, and IGFBP-1, which have been shown to be important factors in growth in utero, may be important in understanding the risk of developing these adult diseases. It would be very important to follow a cohort of children from birth through adulthood with serial measurements of IGF-I, IGFBP-3, and leptin in order to better understand how these factors change over time and how they might contribute to the development of serious adult disorders. Studies such as those by Vatten et al in Norway support the importance of conducting such difficult epidemiological studies.

William L. Clarke, MD

A Longitudinal Study of the Effects of a Gluten-Free Diet on Glycemic Control and Weight Gain in Subjects With Type 1 Diabetes and Celiac Disease

Amin et al from Oxford reported their findings of longitudinal growth characteristics and glycemic control in children with type 1 diabetes along with celiac disease (CD). Annually, from 1994 and 1998, 230 children with type 1 diabetes were screened starting in the first year after the onset for the presence of IgA and anti-endomysial antibodies (EMA). A total of 10 children were EMA positive and another one was AGA positive, which was 4.8% of the clinic population. Only one patient demonstrated symptoms typical of CD, including failure to thrive and steatorrhea; four complained of some mild abdominal discomfort. Jejunal biopsy showed classical histopathology of CD in all eleven patients. These subjects were matched for age, sex, and diabetes duration with two control diabetic children who were negative for EMA. Height, weight, and HbA_{1c} were measured at the time of diagnosis of CD and every 3 months. Antibody levels were tested every 3 months until negative, and then yearly. The ANOVA model was used to determine the influence of CD on both HbA_{1c} and BMI SDS. The data are presented as mean \pm SEM.

Mean BMI SDS in the CD group was significantly lower (-1.2 ± 0.1 vs. -0.1 ± 0.1 , $P=0.005$), as was mean weight SDS (-0.7 ± 0.3 vs. 0.5 ± 0.3 , $P=0.002$) than in those without CD. However, there was no difference between the two groups mean height or C-peptide level. Mean age of diagnosis of CD was 11.2 years (2.2-17.3). The mean duration of diabetes at diagnosis was 3.8 years (0.9-7.2). Mean HbA_{1c} was significantly lower at diagnosis in the children with CD ($8.9\% \pm 0.3\%$ vs. $9.8\% \pm 0.3\%$, $P=0.002$), but there was no difference in the mean daily insulin dose in the two groups. The difference in mean BMI SDS between the subjects and the controls was eliminated by 12 months of gluten-free diet (1.1 ± 0.13 vs. 1.0 ± 0.1 , $P=0.11$). HbA_{1c} levels were lower

than in the controls during the period of gluten-free diet (8.3 ± 0.2 vs. 10.0 ± 0.2 , $P=0.002$). Insulin requirements increased in both groups, but no difference in those requirements developed between the two groups. Using a general factorial linear model, CD was associated with lower BMI SDS and lower HbA_{1c} across time, independent of other factors such as insulin dose and regime. Also, while on a gluten-free diet, the children with CD had lower HbA_{1c} which was independent of BMI SDS or the insulin dose or regimen. The EMA antibodies tended to disappear while the patients were on the gluten-free diets.

The authors reviewed recent reports regarding the association in children between type 1 diabetes and CD. Prevalence rates range between 1.7 to 10%. However the data on whether intervention with gluten-free diet would be of benefit remain controversial. This is, in part, because there are few longitudinal follow-up data and few age and sex matched controlled studies. The authors note that their findings could have been influenced by the small sample size or the increased input by dieticians which was received by case subjects. They stress, that because the long-term complications of CD include gastrointestinal malignancy, lymphoma, infertility, and osteoporosis, the screening of children with type 1 diabetes at a young age may be cost effective and warranted.

Amin R, et al. *Diabetes Care* 25:1117-1122.

Editor's Comment: *These findings are very intriguing. Many pediatric endocrine clinics are now screening children with type 1 diabetes for EMA or tissue transglutaminase IGA to identify CD. There is controversy as to whether or not children who are*