

Editor's comment: These articles document that FGF23 is an important modulator of phosphate homeostasis and that this process is regulated at least in part by PEX through degradation of the growth factor. They further demonstrate that FGF23 levels and resulting phosphate homeostasis can be altered through several mechanisms, including excess production by tumors and by slowed degradation either because the enzyme that normally cleaves FGF23 is ineffective due to mutation or because the growth factor itself is mutated so that it is resistant to degradation. This concept is discussed in depth by Strewler and depicted in the Figure on page 47.

William A. Horton, MD

Strewler GJ. FGF23, hypophosphatemia, and rickets: has phosphatonin been found? *Proc Nat Acad Sci USA* 2001;98:5945-5946.

Second editor's comment: This work illustrates the treasure trove of genetic data already available from the Human Genome Project waiting to be mined for relevance to human physiology and pathophysiology. PEX is expressed by osteoblasts, and it has been hypothesized that "phosphatonin" also may be

synthesized by these cells.¹ In normal mouse embryos, the murine homologue *Fgf23* maps to chromosome 6. The present investigators were unable to demonstrate expression of *Fgf23* in the tibiae of embryonic mice, perhaps suggesting that FGF23 is not "phosphatonin." Tumors that secrete a phosphate-wasting product leading to rickets or osteomalacia have been demonstrated by the same group to express FGF23 mRNA and to synthesize FGF23 protein.² However, it has not as yet been shown that FGF23 has phosphaturic activity or acts upon yet another molecule, the still elusive "phosphatonin."³

Allen W. Root, MD

1. Ecarot B, Desbarats M. 1,25-(OH)₂D₃ down-regulates expression of PHEX, a marker of the mature osteoblast. *Endocrinology* 1999;140:1192-1199.
2. White KE, et al. The autosomal dominant hypophosphataemic rickets (ADHR) gene is a secreted polypeptide overexpressed by tumors that cause phosphate wasting. *J Clin Endocrinol Metab* 2001;86:497-500.
3. Quarles LD, Drezner MK. Pathophysiology of X-linked hypophosphatemia, tumor-induced osteomalacia, and autosomal dominant hypophosphatemia: a perPHEXing problem. *J Clin Endocrinol Metab* 2001;86:494-496. Editorial.

Ethical Issues With Genetic Testing in Pediatrics

Advances in genetic research and emerging genetic technology are enabling testing and screening to be implemented before a full understanding of the ramifications has been developed. Clearly, new developments in genetics should be made available if they promote the best interest of the patient, in this case the child. The Committee on Bioethics of the American Academy of Pediatrics (AAP) reviewed the issues involved in genetic testing and put forward principles that should be considered before genetic testing is provided to an infant, child, or adolescent. Their report cites the Institute of Medicine's report of 1994 assessing genetic risks, implications for health, and social policy in which 3 principles were described for the introduction of new genetic tests: (1) Identification of the genetic condition must provide a clear benefit to the child; (2) a system must be in place to confirm the diagnosis; and (3) treatment and follow-up must be available for the affected individuals.

Although genetic research offers great promise for the improvement of health, the use of genetic testing must be considered carefully and only introduced with full and appropriate informed consent for the parents who provide consent for the child to have testing. There are several critical reasons for this. Genetic testing is different than other types of laboratory testing since the information obtained is familial and thus has implications for other family members. The risks of genetic testing may not be obvious but include psychosocial risks such as guilt, anxiety, and impaired self-esteem, social risks such as stigma, and financial risks involving insurance and employment. Genetic information may have limited predictive power since diseases are very complex and there are multiple environmental and genetic variables. Genetic conditions may be difficult to treat or prevent without additional research. The positive aspects of making a diagnosis should be demonstrated before screening tests are implemented.

The AAP committee report points out that there are insufficient numbers of genetic professionals (genetic counselors and

clinical geneticists) to have primary responsibility for managing the use of genetic testing, and, thus, primary care physicians must become knowledgeable about both the limitations and the positive aspects of genetic screening in children. It is particularly important to provide or refer children for counseling and testing only when it is in the best interest of the child and when testing and counseling can be provided without anticipated harm to the child.

The committee report is broken down into newborn screening, carrier screening, and predictive testing for late-onset disorders. Under newborn screening, it is reiterated that the purpose of newborn screening for genetic disorders is to limit the morbidity and mortality attributable to these inherited diseases. The report indicates that mandatory and voluntary screening should be distinguished. It strongly suggests that informed consent and voluntary screening occur rather than mandatory screening. The informed consent improves the efficiency of response to positive results and incorporates outcomes research if parents are already involved in making the decision to screen. Newborn screening protocols for phenylketonuria and hypothyroidism have been the model for early diagnosis, leading to improved treatable outcomes; however, the evaluation of the consequence of informed refusal is not yet available.

Screening programs to detect carriers are associated with significant concerns about the possibility for communities to misunderstand the carrier state, leading to stigma and discrimination against the identified carrier, as well as the possibility of adverse psychological reactions. Nevertheless, carrier testing for pregnant adolescents or adolescents who plan pregnancies may well be appropriate.

Predictive testing for late-onset disorders is as yet poorly understood and in general should be delayed until an autonomous decision by the individual to have this type of

predictive testing can be made. Reduction in morbidity or mortality as a result of genetic testing for late-onset disorders has not yet been demonstrated, and the risk of adverse psychological response and discrimination by insurers and employers appear to be real concerns. Further, the complexities of genetic testing for complex disorders have not been worked out.

In summary, the AAP Committee on Bioethics points out that pediatricians must be well informed about these issues and understand that there are both positive and negative aspects of genetic screening that are part of proper informed consent. Furthermore, potential harm does exist in screening programs, and testing

should be deferred until adulthood unless there would be significant benefit to the child to undergo genetic testing.

Committee on Bioethics. *Pediatrics* 2001;107:1451-1455.

Editor's comment: *The AAP report on genetic testing should be required reading for pediatricians since there are pitfalls to all genetic testing. These must be understood by both the pediatrician and the person giving permission for testing of a child before testing is undertaken. Therefore, search out the complete article.*

Judith G. Hall, OC, MD

Development of Renal Cell Carcinoma in Living Donor Kidney Grafts (in Association With hGH Administration)

Tyden et al report 2 cases of young boys (~4 years of age) who received kidney transplants from their fathers. De novo development of carcinoma was diagnosed by biopsy 9 and 11 years after transplant. One patient received a new transplant and the other received dialysis therapy. Progressive cyst formation was observed in each kidney for many years before carcinoma was diagnosed. The kidneys remaining in the 2 fathers did not develop cyst formation. The boys received human growth hormone (hGH) for a total of 7 years and approximately 5 years. For the latter, administration was intermittent.

The authors state that although renal cell carcinomas have developed previously in kidney allografts (cadaver source), it is not known whether in those reported cases the carcinomas were de novo or whether they had been present at transplantation. The authors, however, state that these are the first de novo cases reported in living donor transplants. The authors conclude that it is possible that hGH stimulates the growth of renal cell carcinoma, or perhaps induces the development of such carcinoma more quickly, in acquired disease of the kidney transplant. They also state that the findings emphasize the importance of annual ultrasonographic surveillance of renal grafts, especially in the pediatric population.

Tyden G, et al. *Transplantation* 2000;11:1650-1656.

Editor's comment: *Regardless of whether coincident with, or attributable to, hGH administration, the fact that renal cell carcinoma occurred in these 2 kidney recipients who were receiving hGH deserves significant attention. All transplanted patients should be followed closely for the possible development of renal carcinoma. Development of cysts should prompt suspicion that carcinoma might develop. The development of solid tumors superimposed on the cystic kidney should be reason for immediate surgery. The development of cysts in patients receiving hGH, in my opinion, should prompt discontinuation of hGH. Fortunately, the time intervals appear to be lengthy before renal cell carcinoma develops after transplant. The possibility that hGH might be an inductive agent for renal carcinoma, again in my opinion, should be discussed with the parents, and with the child if he/she is the age of consent, before hGH is administered. hGH should be given under the auspices of a research protocol.*

Robert M. Blizzard, MD

Growth Hormone Deficiency (GHD) Caused by Pituitary Stalk Interruption in Fanconi's Anemia

Fanconi's anemia can be associated with growth retardation. The authors describe the presence of isolated growth hormone deficiency (GHD) or GHD associated with thyrotropin deficiency in the pituitary stalk interruption syndrome, which was demonstrated by magnetic resonance imaging (MRI) in 5 patients with Fanconi's anemia. GH treatment produced catch-up growth in all cases. The authors concluded that the combination of these findings suggests a common genetic origin.

Dupuis-Girod S, et al. *J Pediatr* 2001;138:129-133.

Editor's comment: *Fanconi's anemia is a rare autosomal recessive disease of variable penetrance that arises from an abnormal processing of DNA. The first of the genes responsible for this syndrome was identified in this decade (Nature*

1992;358(6385):434). Fanconi's anemia patients may present with multiple congenital abnormalities, including bone marrow failure, and increased susceptibility to cancer. They have a 15,000 times greater risk of developing acute myelogenous leukemia (Blood 1994;84:1650-1655).

It has long been recognized that growth retardation with normal or decreased GH response to pharmacologic stimuli may be present in this disease. The International Fanconi's Anemia registry reported that short stature is a common finding in these patients (mean, 22.37 SDS) with an 81% prevalence of endocrinopathy. Forty-four percent of the tabulated patients had a subnormal response to GH stimulants; 100% had an abnormal response to GH profile (Pediatrics 2001;107:744-754). Dupuis-Girod et al in the present paper