

Importantly, the authors point out that this study was done in the postabsorptive state and, therefore, conclusions with regard to postprandial metabolism cannot be extrapolated from their data. It is hoped that such data will be forthcoming, although such studies are significantly more complex to perform and their data are significantly more complex to analyze.

Arslianian and Kalhan have substantially increased our knowledge with regard to the events that contribute to growth during adolescence.

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Morphogenesis and Tumors "Patched" Together in Gorlin Syndrome

Discoveries related to rare genetic syndromes also may provide insight into common diseases. A case in point is the recent delineation of the molecular defect in Gorlin syndrome, or nevoid basal cell carcinoma syndrome (NBCCS). A predisposition to basal cell carcinoma, medulloblastoma, and ovarian fibroma occurs in this autosomal dominant condition, as do diverse malformations involving the ribs, craniofacial structures, digits, and spine. Many of these manifestations reflect localized overgrowth. The underlying defect turns out to be in a gene called *patched* (*PTC*), which was studied first in fruit flies as an important developmental control gene. A similar defect may be involved in the most common human cancer, basal cell carcinoma of the skin.

Two teams connected NBCCS to *PTC*. Johnson et al¹ started with their work on the fly gene. When they cloned and mapped human *PTC*, they discovered that it resided very close to or where NBCCS had been mapped. Subsequent analysis in 2 families with NBCCS revealed *PTC* mutations. One was a 9-bp insertion; the other was an 11-bp deletion. They also found a point mutation in a basal cell carcinoma not associated with NBCCS.

Hahn and colleagues² used positional cloning to identify *PTC* as the NBCCS gene. Mutations predicted to inactivate *PTC* were found in 6 unrelated NBCCS patients and in tumors from 2 non-NBCCS patients.

Both papers,^{1,2} as well as related editorials,^{3,4} discussed the *PTC* gene product's normal function and its possible role in the pathogenesis of NBCCS and sporadic basal cell carcinoma. In flies, and presumably in humans, *PTC* encodes a transmembrane glycoprotein that acts as an antagonist in the Hedgehog signaling pathway; it influences the effects of a number of growth factors and morphogens, such as members of the transforming growth factor- β and BMP families,

on early embryologic development. Given the inactivating nature of the mutations and the occurrence of tumors in NBCCS, *PTC* must also function as a tumor suppressor gene.

Hahn et al² and Shilo³ speculated that 3 sets of features in NBCCS can be explained by a 2-step mechanism. The first step is the inherited mutation that causes constitutional loss of function at one *PTC* allele, haploinsufficiency; the second step is a sporadic mutation that leads to loss of function at the second allele. They postulated that symmetrical defects, such as craniofacial and overgrowth defects, result from disruption of dosage-sensitive pathways involving *PTC* during early development. Manifestations that are found in random clusters, ie, rib and spine malformations, may reflect sporadic mutations at the second allele in progenitor cells that contribute populations of cells to relevant tissues. Such tissues would be mosaic with regard to *PTC* alleles. Finally, loss of function at the second allele in adulthood leads to basal cell carcinoma and other tumors.

1. Johnson RL, et al. *Science* 1996; 272:1668-1671.
2. Hahn H, et al. *Cell* 1996; 85:841-851.
3. Shilo B-Z. *Nature* 1996; 382:115-116.
4. Pennisi E. *Science* 1996; 272:1583-1584.

Editor's comment: *The authors of all of these reports acknowledge that precisely how PTC acts to influence the Hedgehog signaling pathway and how this pathway works in humans is poorly understood. Nevertheless, it seems clear that PTC influences the proliferation and perhaps survival of cells during development, growth, and carcinogenesis given the clinical manifestations of NBCCS.*

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