Effects of human growth hormone therapy on melanocytic nevus

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Melanocytic nevus may grow more rapidly during human growth hormone (hGH) therapy. With standardised skin photographs, the growth rate of the nevus was two-fold greater in 14 hypophysectomised and 7 Turner's syndrome girls treated with hGH than in untreated patients or controls. HMB-45 immunoreactivity, a marker of stimulated melanocytes, was absent in nevi from 18 of 19 untreated patients, in 4 of 5 hGH treated, and in 8 of 5 Turner's patients studied 2-3 months after stopping hGH. In nevi from 39 hGH-treated patients, showed unusual HMB-45 reactivity in dermal nevocytes. During administration of hGH, melanocytic nevus grow faster and there is reversible stimulation of nevocytes.

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The HMB-45 antibody, which labels actively growing melanocytes, stained melanocytes of rapidly growing nevi excised from a Turner's syndrome patient treated with human growth hormone (hGH). This observation prompted us to study the growth and pathology of melanocytic nevi in hGH-treated patients.

With a vertical Nevi Scanner (Lumea, Malvern, PA, USA), colour slides of the skin were taken every 3-12 months in 23 controls aged 8-16 years, 5 hypophysectomised patients before beginning hGH, and a Turner's syndrome girl of 3 months. We also studied 19 untreated patients with hypopituitarism or Turner's syndrome treated with hGH for 3-6 months. Infected consent was obtained by each patient and their parents. We used a computerised image analyzer (MOP-Videoplan, Kontron). The growth rate was calculated on the basis of 30 measurements each of 13 years 9 months (7.5-11.2) and 9 individuals were prepubertal. Most nevi (5/19) were from areas not exposed to sun. When compared with 24 hypopituitary and 8 Turner's syndrome patients with hypothalamic damage, they showed a significant increase in growth. The distribution of HMB-45 staining was not correlated with growth in height, ranging between 2.5 and 8.5 cm per year, or with pubertal state.

The computed morphometry is accurate and reproducible. Small reductions in size of some nevi could result in repeated measurement in camera position between pictures. The changes in nevi size could not be explained solely by increases in body size. In the fastest growing patients, the 6 months before beginning hGH was associated with only a 3% increase in diameter of the nevus. Although the size and the number of nevi increase up to age 20-30, we found no significant increase in growth in our small series. Turner's syndrome girls develop an increased number of nevi. However, nevus growth rate may be linked to the degree of hypothalamic dysfunction and hypothalamic growth. Thus, a methodological bias, the age-related increase in size, differences in sexual
Drug promotion: stealth, wealth, and safety

One doubts the importance of pharmaceutical marketing and promotion to the drug industry. Promotion and marketing expenditure averages 20-30% of sales turnover,1 or about two to three times the average expenditure on research and development.2 Industry executives themselves freely admit that success depends more on creative marketing than on innovative research.3 Equally, there is no doubt (despite frequent denials from prescribers) that information from drug companies is a powerful influence on prescribing.4 Companies regularly extol the virtues of the high quality of their products but are less virtuous about the quality of the product information they provide. Numerous studies over the past 20 years have provided evidence about substantial information that was incomplete or misleading.5 Companies tend to emphasise the positive aspects of products, focusing on attributes that will give the agent a marketing edge, and not to provide all the objective data (including adverse effects and contraindications) required for comparative analysis.6

The latest study to raise these issues was conducted by the Office of Technology Assessment (OTA) of the US Congress (see June 5, 1993). The OTA found that the label and package inserts for at least half a sample of 241 products sold by US-based companies in four countries—Brazil, Kenya, Panama, and Thailand—failed to provide sufficient information for doctors to use the drugs safely and effectively. The report concludes that reliance on the information provided by manufacturers could lead to "serious or life-threatening problems" or, at best, ineffective treatment.7

A favourite marketing strategy—and one recorded in the OTA study—is to widen the indications for a product. This is not merely a problem in developing countries. Thus, a French government committee described such practices as "commonplace" in 1990,8 while the US Food and Drug Administration regularly takes companies to task over attempts to encourage unapproved uses of drugs.9 10

The OTA study used approved labelling in the USA as a reference guide and also referred to model prescribing information prepared by the World Health Organization (WHO), where this was available for the products under examination. The US Pharmaceutical Manufacturers Association (PMA) has objected to the methods used as "fundamentally flawed" because they did not take into account local health conditions or different medical practices, and has described the findings as "outdated" because the data were collected between 1988 and 1990. According to the PMA, the study was a "snapshot" that ignored the "dynamic" nature of international marketing. However, the OTA report notes that the problems identified in the study cannot be attributed to the result of a time lag in making labelling changes as new information comes to light; the vast majority of the labelling differences concerned information that has been known for some time.

Provision in the OTA report of a summary of some of the major studies of drug promotion and labelling over the years makes for ready comparisons. In fact the OTA snapshot resembles those of other times and other places. For example, a study of advertising in leading medical journals in 18 countries found that important warnings and precautions were missing in half the 6700 advertisements surveyed.10 Taken together, these studies provide a moving picture of too few efforts to achieve an acceptable international standard for drug information.

The OTA report offers the US government several policy options. Since US-based companies are neither better nor worse than their competitors from other countries, some of those options will be applicable elsewhere. There are four broad measures: (a) control at the export level by application of a single standard for labelling information; (b) more efforts to introduce strong international codes and guidelines; (c) support at the import level so that developing countries can strengthen their regulation of pharmaceutical sales and information provision; and (d) continued vigilance and monitoring.

The recommendations for international measures are liable to be the most contentious. The OTA suggests three possibilities that are not mutually exclusive. The first is a code of conduct on pharmaceutical labelling that might borrow some ideas from the International Code of Marketing of