complications with the use of prophylactic fondaparinux in older patients and those with reduced renal function because of the renal clearance of the drug. The best information regarding this comes from the Arixtra for Thromboembolism Prevention in a Medical Indications Study (ARTEMIS),[3] which included 849 subjects with a mean age of 75 years who were randomly assigned to receive prophylaxis with fondaparinux or placebo. Patients with severely reduced renal function (serum creatinine, >180 μmol per liter) were excluded. The rate of major bleeding in both treatment groups was low, at 0.2%. This indicates that fondaparinux has a favorable balance of benefit to risk but should be avoided in patients with severe renal compromise. Famularo et al. also raise the issue of cost, which can be an important determinant in drug choice. However, the cost varies from one market to another and changes with competition, as new drugs become available.

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Somatic *SDHB* Mutation in an Extraadrenal Pheochromocytoma

TO THE EDITOR: As many as 25% of pheochromocytomas — catecholamine-producing tumors located along the sympathetic nervous system, including the adrenals — occur in hereditary tumor syndromes that include von Hippel–Lindau disease (*VHL* gene),[1] multiple endocrine neoplasia type 2 (*RET* gene), neurofibromatosis type 1 (*NF1* gene), and the pheochromocytoma–paraganglioma syndrome (*SDHB* and *SDHD* genes). The last two genes are also associated with extraadrenal pheochromocytoma.[2,3] To date, except for one sporadic *SDHD* mutation, only germ-line mutations in *SDHB* and *SDHD* have been described, even among reported mutations in these genes in apparently sporadic pheochromocytomas and paragangliomas.[4,5]

We present a case of a 25-year-old woman with an extraadrenal pheochromocytoma in the wall of her urinary bladder. Mutational analysis of the pheochromocytoma candidate genes *RET*, *VHL*, *SDHB*, and *SDHD* was performed in tumor and normal DNA present in the same tissue specimen. (The *NF1* gene was not investigated, since the patient had no clinical signs of neurofibromatosis type 1 disease.) A single aberration was found: an *SDHB* 299C→T transition in tumor DNA but not in the patient's normal DNA (Fig. 1A and 1B). This finding was confirmed by allelotyping the DNA samples and repeating the entire procedure, starting with the isolation of DNA from tumor and normal tissue. This somatic *SDHB* gene mutation results in a substitution of phenylalanine for serine at position 100 (S100F). Functional consequences of the S100F mutation can be anticipated, given the large physical differences between the two amino acids: substitution of a nonpolar side chain (F) for an uncharged polar side chain (S). In addition, the region of the *SDHB* gene that includes the S100F mutation is highly conserved at the protein level. Moreover, an *SDHB* germ-line missense mutation of the S100 neighboring amino acid (C101Y) has been described in a patient with an extraadrenal pheochromocytoma.[1]

From the sequence analysis of the tumor DNA, it is apparent that the mutated allele is in excess of the wild-type allele (Fig. 1A), indicating amplification of the mutated allele or loss of the wild-type allele. Comparative genomic hybridization, loss of heterozygosity of the *SDHB* locus (Fig. 1C), and chromosome 1p fluorescence in situ hybridization all showed the loss of one 1p allele. These findings point to the biallelic inactivation of *SDHB* in this tumor: the mutation of one *SDHB* allele and the loss of the second *SDHB* allele. In addition, we found that there was an absence of *SDHB* expression in tumor cells, indicating complete loss of *SDHB* function (Fig. 1D and 1E).

We think it is likely that the somatic S100F mutation played a causal role in the tumorigenesis of the extraadrenal pheochromocytoma. Our

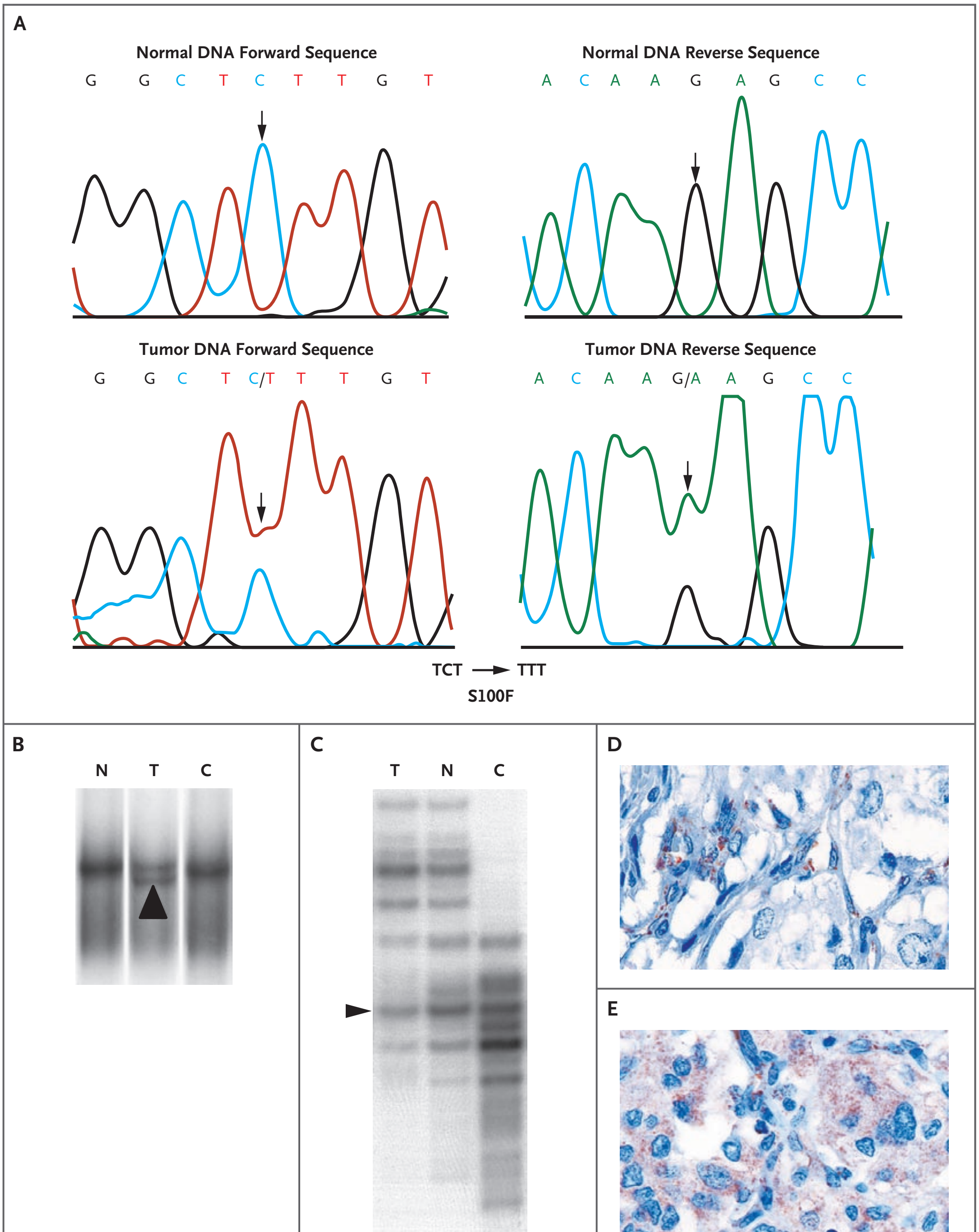

Figure 1. Molecular and Immunohistochemical Results.

Sequencing chromatograms of *SDHB* exon 4 of tumor and normal DNA from the patient show the relative signal intensities at position 299 of the wild-type nucleotide C and the substituted nucleotide T, indicating relative loss of the wild-type allele in the tumor DNA (Panel A). Panel B shows polymerase-chain-reaction–single-strand conformation polymorphism analysis of the patient's normal (N) and tumor (T) DNA, as compared with control (C) DNA from a healthy subject. The aberrant migration pattern in the tumor DNA is apparent (arrowhead). In Panel C, the loss of heterozygosity is shown on an autoradiograph of chromosome 1p with a marker in proximity to the *SDHB* gene, indicating relative loss of tumor DNA (arrowhead), as compared with the patient's normal DNA and control DNA from a healthy subject. Immunohistochemical staining of the patient's tumor for *SDHB* shows unstained tumor cells surrounded by endothelial cells with speckled staining (Panel D), in contrast to the staining pattern in a pheochromocytoma without the *SDHB* mutation (Panel E).

findings suggest that the *SDHB* gene not only plays a role in the pathogenesis of a subgroup of inherited pheochromocytomas but also can be involved in a subgroup of truly sporadic pheochromocytomas.

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Dietary Supplement–Induced Vitamin D Intoxication

TO THE EDITOR: Vitamin D intoxication that is associated with the consumption of dietary supplements is reported rarely.[1] In 2004, the Food and Drug Administration (FDA) learned of the following case.

A 58-year-old woman with diabetes mellitus and rheumatoid arthritis began taking a dietary supplement called Solutions IE Ageless Formula II on January 12, 2004. Fatigue, constipation, back pain, forgetfulness, nausea, and vomiting soon developed. On March 15, 2004, she was hospitalized because her speech was slurred, and a blood glucose reading taken at home was 30 mg per deciliter. On admission, her serum levels were as follows: calcium, more than 3.75 mmol per liter; 25-hydroxyvitamin D, 1171 nmol per liter (normal range, 22 to 135); 1,25-dihydroxyvitamin D, 305 pmol per liter (normal range, 36 to 144); parathyroid hormone, 12 ng per liter (normal range, 10 to 65); calcitonin, 4.5 ng per liter (normal range, 0 to 4.6); albumin, 31 g per liter; phosphorus, 0.81 mmol per liter; blood urea nitrogen, 18.6 mmol per liter; and creatinine, 265 μmol per liter.

The patient was treated with intravenous normal saline, furosemide, and pamidronate disodium. On March 19, 2004, while still hospitalized, she was informed by the product distributor of an error in product formulation such that 188,640 IU of vitamin D_3 had been added to the daily serving size of six capsules instead of the intended 400 IU. At discharge on March 24, the patient's serum levels were as follows: calcium, 2.60 mmol per liter; blood urea nitrogen, 10.0 mmol per liter; and creatinine, 221 μmol per liter. The patient died from a cause unknown to us on January 8, 2005.

Laboratory analysis of the product by the FDA, obtained from one of two lots reportedly overfortified with vitamin D_3, revealed 186,906 IU of vitamin D_3 in each serving size of six capsules, indicating that the patient had consumed roughly 90 times the recommended safe upper limit of 2000 IU per day. Long-term daily vitamin D consumption of more than 40,000 IU (1000 μg) is needed to cause hypercalcemia in healthy persons.[2] In March 2004, the product distributor announced that during the previous month it had received three complaints from customers who had been hospitalized for hypercalcemia and vitamin D toxicity. The same month, the product manufacturer recalled 1600 bottles of the product. The case described here underscores the need for the manufacturers of dietary supplements to