

during these hours. These hours should not be subject to any specific restrictions but should be limited only by the resident's assessment of his or her level of fatigue. If a resident feels it is important to give up an hour on a day off to meet with a patient's family or to stay an extra hour observing an unusual case, it should be allowable. We are required to teach our residents about recognizing fatigue, and this approach would allow us to verify that learning in a supervised setting.

If we fail to make this change to our training

system, we will end up with a large number of medical workers, not medical professionals.

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More on Bevacizumab in Hereditary Hemorrhagic Telangiectasia

TO THE EDITOR: Bose et al. (May 14 issue)¹ report on a patient with hereditary hemorrhagic telangiectasia (HHT) who was treated with bevacizumab for epistaxis. Our patient was a 55-year-old man with HHT (endoglin mutation P.LYS402.FS) with intractable pain and frequent episodes of pancreatitis related to pancreatic arteriovenous malformations. Surgery and embolization were not feasible. An indium-111-labeled bevacizumab single-photon-emission computed tomographic (CT) scan² showed elevated tracer uptake in the arteriovenous malformations. Bevacizumab at a dose of 5.0 mg per kilogram of body weight every 2 weeks was started 1 year ago. This treatment immediately stopped the epistaxis, the skin vascular signs became less pronounced, and the frequency and severity of pancreatitis diminished. After 5 months, the dose was increased to 7.5 mg per kilogram every 2 weeks. Thereafter, morphine and tube feeding could be discontinued, and the patient resumed work. No change in the volume of the arteriovenous malformations was observed on CT. The patient still receives bevacizumab.

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Dr. de Vries reports attending an advisory board meeting for Roche in May 2009 for which the University Medical Center Groningen received €2,000 (\$2,838). No other potential conflict of interest relevant to this letter was reported.

1. Bose P, Holter JL, Selby GB. Bevacizumab in hereditary hemorrhagic telangiectasia. *N Engl J Med* 2009;360:2143-4.
2. Nagengast WB, de Vries EG, Hospers GA, et al. In vivo VEGF imaging with radiolabeled bevacizumab in a human ovarian tumor xenograft. *J Nucl Med* 2007;48:1313-9.

TO THE EDITOR: We administered bevacizumab to a 65-year-old woman with HHT and life-threatening, recurrent hemorrhage. She had undergone liver transplantation 10 years earlier for arteriovenous shunting. Over a 1-year period, worsening anemia developed because of recurrent epistaxis and gastrointestinal bleeding, despite maximal standard therapy of iron infusions, estrogens, and tranexamic acid. From February through July 2008, she received 27 transfusions containing a total of 52 packed cells. Six courses of bevacizumab (5 mg per kilogram) were administered without any adverse events. Blood transfusions were not required for 2 months. Only medical therapy was continued. In December 2008, hemorrhage resumed, but with a reduced need for blood transfusion, as compared with her earlier course.

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THE AUTHORS REPLY: The cases described by Oosting et al. and Retornaz et al. give further

evidence of the efficacy of bevacizumab in patients with HHT. Both cases also show that symptoms and transfusion requirements improve with this therapy, without an appreciable change in arteriovenous malformations. Like Oosting et al., we found no difference in the size of our patient's pulmonary arteriovenous malformations on CT before and after bevacizumab. Their experience demonstrates the long-term safety and tolerability of bevacizumab in such patients. Our patient continues to report symptomatic benefit more than a year after completing therapy, and he has required only one intravenous infusion of iron during this time. His hemoglobin levels have remained stable at 14 to 15 g per deciliter. The cost

of our patient's regimen (a total of 30 mg per kilogram over four cycles) would be approximately \$12,000 today. The costs of continuing the drug in the long term, especially without a Food and Drug Administration–approved indication, would be prohibitive. Our case shows that intermittent dosing allows for long-term, symptomatic improvement and stability of pulmonary arteriovenous malformations.

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Renal Sympathetic-Nerve Ablation for Uncontrolled Hypertension

TO THE EDITOR: The renal sympathetic nerves have been identified as a major contributor to the complex pathophysiology of hypertension in both experimental models and in humans.¹ Patients with essential hypertension generally have increased efferent sympathetic drive to the kidneys, as evidenced by elevated rates of renal norepinephrine spillover, defined as the amount of transmitter that escapes neuronal uptake and local metabolism and thus “spills over” into the circulation. Hypertension is also characterized by an increased rate of sympathetic-nerve firing, possibly modulated by afferent signaling from renal sensory nerves.²⁻⁴

A 59-year-old male patient with long-standing essential hypertension that was resistant to pharmacologic treatment with seven different antihypertensive drugs underwent catheter-based radiofrequency ablation to excise renal nerves that carry both efferent sympathetic and afferent sensory fibers. The patient had a history of two transient ischemic attacks and sleep apnea that was untreated because of an inability to tolerate therapy with continuous positive airway pressure. Secondary forms of hypertension and heart failure were excluded. The mean office blood pressure was 161/107 mm Hg, with a heart rate of 76 beats per minute at baseline.

Radiofrequency ablation was applied to both renal arteries without apparent procedural com-

plications. There were no vascular or subsequent biochemical complications, and renal function was unaltered. Renal norepinephrine spillover, as assessed by the radiotracer dilution method^{2,4} from both the left and right kidneys, was approximately three times the normal level at baseline (72 and 79 ng per minute, respectively). Bilateral renal-nerve ablation resulted in a marked reduction in renal norepinephrine spillover from both kidneys, with a reduction of 48% from the left kidney and 75% from the right kidney, which demonstrated the effectiveness of the intervention (Fig. 1A). This effect was accompanied by halving of renin activity (from 0.30 to 0.15 μ g per liter per hour), an increase in renal plasma flow from 719 to 1126 ml per minute, and a progressive and sustained reduction in systemic blood pressure from 161/107 mm Hg at baseline to 141/90 mm Hg at 30 days to 127/81 mm Hg at 12 months. Whole-body norepinephrine spillover was reduced by 42% (Fig. 1B).

Microneurography at baseline and at 30 days and 12 months showed a gradual reduction in muscle sympathetic-nerve activity to normal levels (56, 41, and 19 bursts per minute, respectively) (Fig. 1C). We also observed an improvement in cardiac baroreflex sensitivity after renal denervation (from 7.8 to 11.7 msec per millimeter of mercury). Cardiovascular magnetic resonance