Letters to the Editor

Letters to the Editor are welcomed. They may report new clinical or laboratory observations and new developments in medical care or may contain comments on recent contents of the Journal. They will be published, if found suitable, as space permits. Like other material submitted for publication, letters must be typewritten, double-spaced, and must not exceed two typewritten pages in length. No more than five references and one figure or table may be used. See “Information for Authors” for format of references, tables, and figures. Editing, possible abridgment, and acceptance remain the prerogative of the Editors.

Overlooked Aspartame-Induced Hypertension

To the Editor: As a constructive comment on the excellent article by Trewet and Ernst1 on “resistant hypertension,” allow me to mention an important factor contributing to hypertension that continues to be overlooked: “diet” products containing aspartame which are being consumed by an estimated two-thirds of the population.

I reported earlier on hypertension in 64 aspartame reactors who were not known to have had an elevated blood pressure prior to using this chemical.2 Its severity was impressive—eg, a registered nurse with readings as high as 280/160. The blood pressure in another nurse rose to 240/150. Several patients were studied to rule out pheochromocytoma. The causative role of aspartame products was indicated by 1) the striking improvement or normalization of blood pressure after stopping aspartame, and 2) the prompt recurrence of hypertension following aspartame resumption.

The association of hypertension with the consumption of cola beverages (Diet Coke™, Diet Pepsi™) has been confirmed by Winkelmayer et al3 in a large prospective study of female nurses—but NOT with caffeine consumption. They speculated that “perhaps some other compound contained in soda-type soft drinks . . . may be responsible for the increased risk of hypertension.”

I have reviewed the likely pharmacologic basis, especially the conversion of phenylalanine (comprising half of the aspartame molecule) to dopamine, epinephrine, and norepinephrine . . . all pressor substances.2 Other aspartame reactors have evidenced peripheral vasomotor features (including the Raynaud phenomenon),2 and probable pulmonary hypertension.4

At the very least, persons with hypertension that resist conventional therapy ought to avoid aspartame products.

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References

Serious Cardioembolic Stroke Resulting from an Overlooked Left Ventricular Noncompaction

To the Editor: Left ventricular hypertrophy/noncompaction (LVHT) is a rare congenital cardiomyopathy that remains frequently overlooked and is known to have an increased tendency to lead to thromboembolic events.1 Because of the serious potential for cardiovascular complications, early recognition is essential. We report the case of a 14-year-old boy with Down syndrome who developed an acute cardioembolic stroke during hospital admission for heart failure. Three years previously, he had undergone surgical repair of a ventricular septal defect (perimembranous type), and a permanent pacemaker was implanted due to complete atrioventricular block after repair. During follow up, progression of aortic regurgitation was noted; the left ventricular cavity had become dilated and systolic function had worsened.

Recently, the patient was admitted due to dyspnea on exertion (New York Heart Association functional class III). On physical examination, he had a diastolic murmur in the left parasternal area (grade IV/VI). On the tenth hospital day,

Fig. Transthoracic echocardiogram performed during the current admission; parasternal short-axis view at left ventricular apex (zoom) shows an extensive trabeculated layer of myocardium and multiple deep intertrabecular recesses (arrows).
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he developed an acute left-sided hemiparesis. Computed tomography and angiography of the brain demonstrated occluded right middle cerebral artery (MCA) with hyperacute infarct along the right MCA territory. Transthoracic echocardiogram demonstrated a markedly dilated left ventricle (LV) with severely impaired systolic function (LV end diastolic diameter 83 mm; LV ejection fraction 20%). His aortic valve had severe aortic regurgitation due to malcoaptation between the noncoronary and right coronary cusp. Also, there was a spongy-like subendocardial layer with prominent trabeculation, suggestive of LVHT (Fig.). Intracardiac thrombus was not detected. The preoperative transthoracic echocardiogram performed three years previously was retrospectively reviewed and LVHT was noted. The LV systolic function and cavity size were normal. This case report shows that physicians and echocardiographers must be aware of LVHT in order to prevent any delay in diagnosis. Because of the serious potential for cardiovascular complications, early recognition is essential. Prophylactic anti-coagulation should be considered to prevent embolic stroke when the ventricular systolic function has begun to deteriorate.

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of HPO is not completely understood, but the presence of arteriovenous shunts (either in the heart or in the lungs) seems to be condicio sine qua non. We support this hypothesis by describing a patient with nonsmall cell lung cancer who had HPO at the time of diagnosis, but not at the time of extrapulmonary relapse.

HPO may be found in a number of medical conditions, including lung cancer or lung metastases, congenital cyanotic heart disease, liver cirrhosis, and other systemic illnesses with pulmonary involvement. HPO regresses with effective treatment of the malignancy. Symptomatic treatment may include the use of nonsteroidal anti-inflammatory drugs, bisphosphonates, or octreotide.

A 71-year-old female was diagnosed with nonsmall cell lung cancer (NSCLC) stage IIIA. She underwent a whole body bone scan, which was compatible with HPO. The patient was treated with platinum-based chemotherapy, radiation to the right chest and mediastinum, and had a right lower lobectomy and right upper lobe wedge resection. Six months later, she developed metastatic lesions in the brain confirmed by magnetic resonance imaging. Computed tomography scans of her chest, abdomen, and pelvis were negative. Her bone scan was repeated and showed stable focus in the left glenohumeral region, but HPO had resolved. No findings were highly suspicious for metastatic disease to the bone.

Since its original description by Hippocrates in the fifth century BC, the strong association of digital clubbing and HPO with serious disease has been a clinical enigma. There is both indirect and direct evidence that a substantial number of megakaryocytes arrest in the pulmonary capillary bed and release platelets at this site. Thanks to arteriovenous shunts (either in the heart or in the lungs) these circulating megakaryocytes or their fragments reach the fingertips in the axial vascular stream, releasing factors such as vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF), which induce the stromal and vascular changes present in HPO. This explains why there were no signs of HPO recurrence when our patient developed brain metastases, as HPO requires intrapulmonary arteriovenous shunting.

As anti-VEGF monoclonal antibodies (eg, bevacizumab) and VEGF pathway inhibitors (several drugs in different phases of clinical trials) become more frequently used in the clinical practice of various cancers, it is likely that we will learn more about the pathogenesis of HPO in the near future.

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Long-Term Survival After Glioblastoma Multiforme

To the Editor: Glioblastoma multiforme (GBM) is the most aggressive of primary brain tumors with a median survival of approximately 12 months; fewer than 25% of patients survive up to 2 years and fewer than 10% up to 5 years. We report a very rare case of a patient who survived for 12 years following diagnosis of GBM. The patient, a 65-year-old African-American woman, was brought to the emergency room in October 2007 because “she was not acting right.” Her speech was very low and incomprehensible. She looked weak, somnolent, and slightly more lethargic than her usual self. Past medical history was remarkable for GBM 12 years previously. In April 1995, a 3 cm ring-enhancing lesion was detected by magnetic resonance imaging (MRI) in her right temporal lobe. Pathology showed GBM with sarcomatoid features. The patient was treated with surgery, radiation (6000 rads) and chemotherapy with BCNU (Carmustine). She also had intra-arterial chemotherapy given at the tumor site using femoral catheterization. She was then lost to followup until recently.

MRI with and without contrast showed a focal 4.6 × 3.5 × 3.0 cm left frontal lobe subcortical and deep white matter-enhancing mass with central seepateation and internal fluid. Vasogenic edema surrounding the left frontal lobe was extended into the anterior left corona radiata and the anterior limb of the left internal and external capsule. There was left to right subfalcine herniation with bifrontal lateral hemispheric mass effect and effacement. These findings could be due to a new tumor or cerebral necrosis. Unfortunately, the patient and her family decided not to do a biopsy. She was then lost to follow-up. Hospital records show that on April 4th 2008 she was brought to the ER because she fell from a chair which meant the patient was still alive 13 years after the initial GB diagnosis.

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Despite extensive clinical trials, individual prediction of clinical outcome has remained an elusive goal. Reports of living more than 10 years after GBM are very rare. Patient survival depends on a variety of clinical and biologic parameters including tumor size and location, younger age (<40 years), functional status at presentation (Karnofsky score), aggressive surgical and multimodal treatment including radiotherapy and chemotherapy (temozolomide), histologic indicators (lower mitotic index), and genetic markers O-6-methylguanine-DNA methyltransferase (MGMT) gene silencing.

A potential problem in these patients is cognitive decline after treatment. In one study, long-term survival was frequently accompanied by severe treatment-induced dementia. However, in another study, attention, construction, and arithmetic abilities were impaired, but the level of functioning, Karnofsky score, and overall quality of life were stable.

In conclusion, GBM patients can, in rare cases, survive over 10 years; however, the risk of residual functional difficulties is significant.

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Hydrocortisone in Severe Sepsis: Time to Accept the Null Hypothesis?

To the Editor: The use of glucocorticoids in severe sepsis has had its fair share of controversy. In the 1960s, studies in animal models suggested that steroids might have survival benefits in sepsis and paved the way for trials with large doses. By the mid-1990s, meta-analysis disproved the efficacy of large doses of steroids with secondary infections due to the attendant immunosuppression becoming a concern.

A belief emerged around this time that the loss of response of the adrenal gland to corticotropin injection in septic patients was etiologically related to the hemodynamic instability of sepsis and mortality. As a result, the concept of adrenal replacement therapy with low-dose corticosteroids was born. The belief that nonresponders were those who would benefit from corticosteroid therapy was reinforced by a meta-analysis by Minneci et al supporting low-dose hydrocortisone in divided doses for patients on vasopressor support and in corticotropin-negative responders, provided the steroids were administered for a minimum of 5 days followed by a tapering period of 5 to 7 days.

The new publication of a multicenter, randomized, controlled and double-blinded study by Sprung et al at the beginning of 2008 is the latest in a growing list of dissenters. This study concluded that hydrocortisone did not demonstrate survival improvement in severe sepsis when compared with placebo. The study also failed to show proof of shock reversal either in the overall patients or in the corticotropin-nonresponding subgroup, although it hastened the reversal of shock in those in whom shock was reversed.

Armed with mounting statistics on a specific treatment for a particular pathology in the same species, how could we have failed to reach consensus for so long? Regardless of the era of publication, it has to be assumed that clinical investigators in this subject gave it their best efforts and meant well for their patients. Yet questions remain unanswered. We surmise that the missing link in this controversy is bias. Previous publications have probably been tainted with selection bias, while publication bias misused meta-analyses based on those studies.

The pharmaceutical industry has not been particularly benevolent in funding research and, therefore, one has to wonder whether the financial influence it has in clinical trials may not have contributed to this clinical perplexity. Now that we are tending toward accepting the null hypothesis, future trials need to have more stringency to prove that hydrocortisone impacts beneficially in sepsis.

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Ischemic Colitis, An Unusual Complication of Colonoscopy

To the Editor: Ischemic colitis is a characteristic disease of the large in-
Ischemic colitis caused by varying degrees of anatomic or functional vascular insufficiency. Colonoscopy is the gold standard for the identification of colonic ischemia; however, very rarely, colonoscopy itself may induce ischemic colitis under certain conditions. A 34-year-old woman who had iron deficiency anemia was admitted to our gastroenterology department for colonoscopic examination. Colonoscopy was completely normal. Seven hours after the colonoscopy, she developed bloody diarrhea and mild abdominal pain. An abdominal examination was normal other than lower abdominal tenderness. Hemoglobin did not decrease. Stool microscopy showed erythrocytes, and a culture revealed normal flora. Plain abdominal radiography and abdominal ultrasonography were both normal. A repeat colonoscopy was performed and showed patchy hemorrhagic, edematous, and thickened mucosa, with superficial ulceration extending from the proximal rectum to the splenic flexure. Histologic analysis was compatible with ischemic colitis. Tests for antinuclear antibodies, anti-DNA antibodies and antimitochondrial antibodies were negative. Over the next two days, the patient’s abdominal pain and bloody stools improved gradually. On the fifth day, colonoscopy revealed normal colon mucosa. She was free of complaints at her four month follow-up visit.

Ischemic colitis presents as a spectrum of injury from transient ischemia involving the mucosa and submucosa to acute fulminant necrosis that may progress to death. Although there is a variety of causes, two main mechanisms may lead to bowel ischemia: reduced bowel perfusion because of low cardiac output, or occlusive disease of the bowel vascular system. However, the actual cause for the ischemia may not always be identified. Ischemic colitis very rarely occurs as a result of colonoscopic examination. Underlying connective tissue disorders are often the predisposing factors in those cases.

Cremers et al reported colonoscopy-induced ischemic colitis in a patient without an underlying predisposing factor. Our patient developed ischemic mucosal injury secondary to colonoscopy. She had no risk factors, including connective tissue disorders, or drug intake, including oral contraceptives. She also did not have intra-procedural hypotension or a history of gastrointestinal or systemic disease.

Three mechanisms may have contributed to the colonoscopy-induced ischemic colitis in our present case. First, overdistention of the large bowel with air might have reduced colonic blood flow and thus caused a shunting of blood from the mucosa to the serosa, consequently producing colonic ischemia. Second, the mechanical effect of the colonoscope body on the colon wall may have led to diminished mucosal blood flow. Third, transient torsion of the colonic vascular system resulting from exaggerated pulling back and shortening might have reduced the blood flow.

The prognosis in colonoscopy-induced ischemic colitis usually has been reported as good, but ischemia with necrosis may extend into the deep layers of the bowel wall and impair the colonic barrier against microorganisms. Thereby, it may increase mortality and morbidity, particularly in patients with comorbid diseases, immunodepressive disorders, or compensated mesenteric ischemia.

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