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## DECREASED CORONARY RESERVE AND ANGINA PECTORIS IN AORTIC STENOSIS WITH NORMAL CORONARY ARTERIES

*To the Editor:* The study by Marcus et al. (Nov. 25 issue)[1] describes intraoperative determinations of coronary vascular reserve in patients who allegedly had hypertrophic ventricles. There are problems with the study in that the patients were all heparinized (which itself affects coronary flow) and not under the usual physiologic conditions. Thus, only comparison between the control patients and the patients with aortic stenosis was possible. The authors do not report any gradation of response in relation to the degree of hypertrophy, nor do they attempt to quantify hypertrophy. Finally, they should have done multivariate analysis to determine whether the lack of hyperemic flow response was related to the hemodynamic load at the time — i.e., to left ventricular systolic pressure — or to left ventricular mass or other factors. The authors commented that because Pichard et al.[2] did not use a maximal coronary dilatory stimulus — i.e., angiographic contrast medium — the study was "inadequate." Although this was clearly recognized by the investigators in that study, they were nevertheless able to show striking differences with this vasodilator probe in elicited reserve flow between normal patients and those with hypertrophic ventricles. More important, however, their results both in aortic stenosis and in aortic regurgitation showed that beyond a certain point left ventricular mass and coronary vascular reserve correlated inversely as a continuous variable. Finally, from a historical point of view, decreased coronary blood flow in response to stress with production of lactic acid was demonstrated by Fallen et al. in 1967 in patients with aortic stenosis.[3]

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1. Marcus ML, Doty DB, Hiratzka LF, Wright CB, Eastham CL. Decreased coronary reserve: a mechanism for angina pectoris in patients with aortic stenosis and normal coronary arteries. N Engl J Med 1982; 307:1362-6.
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The above letter was referred to the authors of the article in question, who offer the following reply:

*To the Editor:* We apologize for our oversight in not citing an important study in this area of research by Fallen et al.[1] from Dr. Gorlin's laboratory. Dr. Gorlin's letter raises three concerns about our study that should be addressed.

Could the use of heparin have influenced our results? In patients, a bolus intravenous infusion of 5000 units of heparin increases coronary blood flow by about 15 per cent.[2,3] This degree of coronary dilation is far smaller than the 500 per cent increase in coronary flow we found in response to the 20-second coronary occlusions we used in our study. Thus, it is doubtful that the heparin could have influenced our data to any important extent. In addition, both the control group and the patients with aortic stenosis received similar doses of heparin in our study and in the study of Pichard et al. from Dr. Gorlin's laboratory.[4]

Could alterations in left ventricular systolic pressure have influenced our data? Although left ventricular systolic pressure markedly affects myocardial oxygen consumption and extravascular compressive forces, two studies from our laboratory[5,6] have shown that moderate alterations in left ventricular systolic pressure have no major effect on coronary reactive hyperemia responses or minimal coronary vascular resistance in hypertrophied ventricles. In particular, we have reported[6] that coronary reactive hyperemia responses in children with supravalvular aortic stenosis were similar before and after substantial relief of left ventricular outflow obstruction.

Does the impaired coronary reserve noted in our patients with aortic stenosis correlate with the severity of left ventricular hypertrophy? In the study by Pichard et al.[4] a weak negative correlation ($r = -0.51$) was noted between coronary reserve and left ventricular mass in patients with aortic stenosis. However, in our opinion, the technique used to measure coronary reserve was inadequate. In our study, in which coronary reserve was measured accurately, the correlation between left ventricular mass, as measured by echocardiography, and coronary reserve in patients with aortic stenosis was even less than that reported by Pichard et al.[4] ($r = -0.25$). This correlation was not significant at the 0.05 level of confidence. We chose not to report this weak correlation in our paper. In our view, it is somewhat simplistic to assume that the severity of hypertrophy is the principal or sole determinant of the impairment in coronary reserve that is observed in patients with enlarged hearts. A recent review[7] suggests that at least five factors other than the severity of cardiac hypertrophy are involved in the interaction between the growth of cardiac muscle and coronary vascular reserve: the stimulus to cardiac hypertrophy (volume versus pressure-induced hypertrophy, and so forth), the age at which the stimulus is applied, duration of the hypertrophy, right ventricular hypertrophy versus left ventricular hypertrophy, and species differences. The importance of the extent of hypertrophy itself in limiting coronary reserve awaits further definition and appears to vary in different models.

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## NEUROTOXICITY OF BACTERIOSTATIC WATER

*To the Editor:* Gershanik et al. (Nov. 25 issue) point out the potential toxicity of benzyl alcohol in bacteriostatic saline and water given to neonates.[1] We have recently reported a case that illustrates the toxicity of bacteriostatic water given intrathecally.[2]

A 64-year-old man with lymphomatous meningitis had flaccid paraplegia that rapidly developed after intrathecal injection of 100 mg of cytarabine inadvertently dissolved in 5 ml of bacteriostatic water containing 1.5 per cent benzyl alcohol. This neurologic deficit was reversed by rinsing the cerebrospinal-fluid space with 0.9 per cent sodium chloride. Intrathecal injections of cytarabine dissolved in sterile distilled water before and after the above episode caused no neurologic symptoms. The patient died of systemic lymphoma

six months later. Autopsy showed fibrosis of the cauda equina with a patchy distribution of thinly myelinated fibers in the dorsal and ventral roots, indicative of repaired segmental demyelination. There was no lymphomatous infiltrate.

We studied the effects of bacteriostatic water and saline in rats. Intrathecal injections of 50 μl of bacteriostatic saline or water (1.5 per cent benzyl alcohol) produced histologic evidence of both demyelination and axonal degeneration in the cauda equina. Physiologic studies in rat nerve roots showed that bacteriostatic saline and water had both a local anesthetic effect and an irreversible toxic effect on nerve conduction.

The local anesthetic and toxic effects of the diluent bacteriostatic water and of preservatives, such as methylhydroxybenzoate,[3] often added to methotrexate, may explain many of the reported cases of paraparesis after intrathecal chemotherapy.[4,5] We recommend that bacteriostatic saline or water often packaged with chemotherapeutic drugs be discarded, and that sterile saline or preferably the patient's own cerebrospinal fluid be used to dilute the drugs. Of the three forms of methotrexate available, only preservative-free lyophilized methotrexate sodium should be used intrathecally.

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## MECHANISMS OF GASTROESOPHAGEAL REFLUX

*To the Editor:* The article by Dodds et al. (Dec. 16 issue)* was particularly lucid, but it failed to mention one mechanism for gastroesophageal reflux that I see very commonly among symptomatic patients. Many such patients intentionally belch ("burp") frequently during the day in order to relieve their symptoms or their concerns. Many of them will burp 25 to 100 times per day. If they have been doing this for only a brief period and fewer than 25 times per day, they can usually respond to instructions to try to cease this habit, and understand an explanation that it is aggravating their symptoms. If it has gone on for a year or more and has reached 100 times per day, it is often a habit that they cannot break. Among the mechanisms of gastroesophageal reflux described by Dodds et al., intentional burping is most similar to intra-abdominal pressure transients.

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*Dodds WJ, Dent J, Hogan WJ, et al. Mechanisms of gastroesophageal reflux in patients with reflux esophagitis. N Engl J Med 1982; 307:1547-52.

The above letter was referred to the authors of the article in question, who offer the following reply:

*To the Editor:* We agree with Dr. Moore's observation that overt "burps," or belches, occur frequently in some patients with reflux esophagitis. These burps may escape detection unless the patient is observed closely or thoroughly questioned. Belching may occur when the basal pressure of the lower esophageal sphincter (LES) is virtually zero, when a feeble LES is challenged by a transient increase in intragastric pressure, or more commonly during a transient complete LES relaxation.

The temporal profile of the transient LES relaxations associated with reflux suggests nerve mediation, although the putative inhibitory motor nerves and triggering sensory stimuli remain to be elucidated. Transient relaxations, comparable to those that lead to reflux, may be simulated in animals by rapid repetitive swallows, esophageal distension, and appropriate vagal stimulation. Our data drawn from feeding and other methods indicate that the rate of transient complete LES relaxations, and thus the rate of reflux, is increased by gastric distension. In many respects the transient LES relaxations associated with acid reflux are comparable to those that accompany belching, and may be identical. Perhaps an abnormal rate of acid reflux occurs when the LES cannot sample normally between gas and liquid. Unduly high rates of LES relaxations may be caused by a low threshold of a "belching reflex," increased sensory stimuli, anatomic deformity, or other factors. The complete explanation is probably complex, and a single mechanism will undoubtedly not suffice for all patients.

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## CRYPTOSPORIDIAL CHOLECYSTITIS

*To the Editor:* Cryptosporidiosis, a protozoan zoonosis affecting the microvillus layer of gastrointestinal cells, has recently been recognized as a cause of diarrhea in immunocompromised patients.[1] Cryptosporidial involvement of the biliary tract has been only exceptionally reported in animals.[2] We describe a patient with the acquired immune-deficiency syndrome complicated by extensive gastrointestinal cryptosporidiosis, in whom the gallbladder was also found to be affected by this parasitic infection.

A 33-year-old homosexual man who had had diarrhea for seven months with fever, abdominal pain, and weight loss was found to have laboratory evidence of cholestasis. Computerized tomography of the abdomen and endoscopic retrograde cholecystopancreatography demonstrated dilation of the common bile duct. An exploratory laparotomy revealed a stenotic papilla as the cause of the cholestasis and a chronically inflamed gallbladder, which was resected. The patient was also found to have Kaposi's sarcoma involving mesenteric jejunal lymph nodes. Postoperatively, a diagnosis of gastrointestinal cryptosporidiosis was established by examination of mucosal biopsy specimens obtained endoscopically from the prepyloric area and distal colon and by the subsequent discovery of cryptosporidial oocysts in the feces. In the light of this finding a review of the operative specimen revealed that the mucosa of the gallbladder was heavily infected with cryptosporidia as well. In spite of several different forms of therapy (furazolidone, trimethoprim–sulfamethoxazole, bismuth subsalicylate, and diphenoxylate hydrochloride), the diarrhea has persisted, with a volume of up to 6 liters per day.

Since the first description of human cryptosporidiosis in 1976,[3] approximately 30 cases have been reported, most of them complicating the acquired immune-deficiency syndrome.[1] In all circumstances the parasitic infection was considered to be restricted to the gastrointestinal tract. Discovery of this organism in the gallbladder suggests the possibility of disseminated infection. Unfortunately, therapeutic trials have failed to eradicate this infection in immunodeficient patients. The fact that this organism can affect the gallbladder raises the potential question of a chronic carrier state.

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