square of the diastolic flow rate. The latter inevitably rises during tachycardia since the absolute diastolic time interval decreases at faster heart rates.

A second case history documented similar improvement in a patient with mitral regurgitation (MR) whose rapid ventricular rate also was controlled (180 to 65 beats/min) with verapamil. However, the author’s generalization that “compensation for mitral regurgitation may be impaired seriously by tachycardia” is not supported by the known physiologic determinants of the mitral regurgitant volume. Retrograde flow across the mitral valve is directly related to the product of the regurgitant orifice size and the square root of the systolic pressure gradient between the left ventricle and left atrium. Therefore, unless the entire mitral valve complex is rigidly calcified, the regurgitant orifice area can change in size. This will alter the regurgitant volume to a greater degree than similar changes in the systolic pressure gradient. Studies using different methods of changing ventricular size have demonstrated alterations in the regurgitant volume. For example, in dogs with acute MR, volume loading increases the regurgitant volume without altering the systolic ventriculoatrial pressure gradient. Conversely, positive inotropic agents such as digitalis decrease regurgitant volume by reducing ventricular size. Isoproterenol also decreases the volume of retrograde flow in dogs with acute MR despite a significant increase in heart rate. A decline in the regurgitant fraction also has been observed during exercise-induced tachycardia in patients with chronic MR. While concurrent sympathetic stimulation may augment contractility as well, the faster (smaller) heart should provide for a smaller regurgitant orifice. Regurgitation due to mitral valve prolapse is an important exception. In this condition, reductions in ventricular volume will enhance leaflet redundancy and thereby exacerbate regurgitant flow.

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In reply— I appreciate Dr. Jackson’s comment on my case report.

No clinical evidence exists to suggest that tachycardia would be beneficial in relieving pulmonary congestion induced by heart failure in patients with chronic mitral regurgitation associated with atrial fibrillation. In experimental animals (dogs), norepinephrine administration was shown to decrease the regurgitant fraction by decreasing mitral orifice area. Whether such a mechanism does exist in patients remains uncertain at present. In severe mitral regurgitation in dogs, isoproterenol decreases left atrial pressure and diameter by restoring more forceful atrial shortening. Since the dogs in this experiment were not in atrial fibrillation, the beneficial effect of isoproterenol was attributed to increased atrial contraction but not to the tachycardia. That the isoproterenol also decreased the volume of retrograde flow in dogs with acute mitral regurgitation despite tachycardia cannot be applied to our patient either.

I am not sure whether Dr. Jackson suggests that tachycardia should not be treated or that we should either use isoproterenol or levophed.

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(Corrected for publication September 23, 1983.)

Cimetidine—Unresolved Issues

To the Editor:—The recent editorial by Moir1 states that “there is now justification for replacement of oral antacid by cimetidine before elective cesarean section.” Furthermore, in the original paper, Hodgkinson et al.2 confirm that cimetidine crosses the human placenta in large amounts.3 Both of these points must be addressed.

First, cimetidine has not been recommended by the FDA for use in pregnant or nursing women or children under 16 years of age. Are we justified from a medicolegal viewpoint in using this drug if no added benefit has been clearly documented?

Second, although Apgar and neurobehavioral scores are apparently unaffected,2 potential long-term side-effects have not been ruled out. A report by Glade et al.4 described a transient rise in liver enzymes in a newborn exposed to cimetidine before birth. Furthermore, as demonstrated by Goetzman and Milstein,5 tolazoline, a dilator of pulmonary vasculature, acts as an H2-receptor agonist in the lung. It is yet to be determined whether cimetidine, by way of its action at the H2 receptor, contributes to increased pulmonary vascular resistance in the newborn.

We believe that both of these questions must be resolved before cimetidine is introduced into routine use in obstetrics.

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In reply.—Drs. Berman and Patel raise some important points in their letter and I am grateful for the opportunity to answer them.

There is no doubt that cimetidine crosses the placenta in substantial amounts but that Apgar and neurobehavioural scores apparently are unaffected. The apparent safety of cimetidine and the allied agent ranitidine has now been confirmed in several thousand cases in the United Kingdom when given during labor or before elective cesarean section. The question now raised is whether and in what circumstances cimetidine administered to the mother causes a transient rise in neonatal hepatic enzymes. In the case reported by Glade et al. and referred to by Berman and Patel the infant weighed only 1,676 g when delivered by the breech at 37 weeks gestation, subsequently developed jaundice and hepatomegaly, but was clinically well when 60 days of age. The mother had received 1,200 mg cimetidine daily for one month before