In reply.—We have read with interest the letter by Hirshman et al., and are frankly somewhat puzzled by the point they are attempting to make.

We are specified specifically for suggesting a relationship between histamine release and cardiovascular effects. To bolster their argument they inappropriately refer to data we published concerning an anaphylactoid reaction following succinylcholine which did not involve significant hypotension. If they would care to re-read the article, they will note that 1,500 ml of lactated Ringer's solution was infused rapidly to avoid hypotension. Nonetheless, there was a rapid and profound decrease in SVR.

The relationship between histamine release, not involving anaphylaxis, and decrease in SVR is certainly significant, as we and others have reported. We agree that our correlation of SVR as an isolated report does not necessarily imply causation. However, when the effect on SVR can be prevented by histamine antagonists as we reported, it seems reasonable and prudent to conclude a causal relationship exists. We agree that this technique is far from perfect, but it is the classic and universally accepted method of determining causality.

The histamine antagonists had no significant effect on SVR. Furthermore, when heart rate is not affected, comparable results are obtained. We have also obtained the same results when chlorpheniramine is substituted for diphenhydramine and there is no increase in heart rate. The suggestion about atropine borders on the ridiculous.

It appears that Hirshman et al. accept that morphine can decrease SVR, that morphine can cause histamine release, and that histamine can cause a decrease in SVR. We have demonstrated that histamine antagonists prevent much of the decrease in SVR associated with morphine as well as other histamine-releasing drugs.

We appear to have a webbed and billed bird that quacks. It might be a canary in disguise, but it seems more realistic to call it a duck.

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REFERENCES


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In reply.—I have several comments to make in response to the letter by Hirshman, Downes, and Butler.

I agree with the authors about the need for more evidence, but in reference to my editorial, I take exception to their comment: "we are unable to determine the patient population underlying this statement since all 3 references refer to the same patient." One of the references was to Lorenz and associates, who have carefully documented eight cases of drug-induced reactions associated with histamine release. My monograph in-
cludes references to our earlier studies on 24 patients with basophilia, mastocytosis, and urticarial reactions, four of whom had elevated plasma histamine levels and were symptomatic. Since then, an additional 12 patients have been studied, and to date, nine patients with episodes of elevated histamine levels have been detected. The experience with this population was the basis of my statement.

In regard to the studies of Moss et al., Hirshman, Downes, and Butler failed to mention that an infusion of 1.5 l lactated Ringer's solution was required to maintain venous pressure, and that systemic vascular resistance declined from 1,000 to 698 dyne·s·cm⁻². They also interpret the work of Smith et al. somewhat differently than the authors who noted: "although plasma histamine levels were not related to cutaneous reactions, the plasma histamine levels correlated with the severity and duration of cardiopulmonary changes during anaphylactic shock." The mean plasma histamine levels (ng/ml) reported by Smith et al. were: normals, <1, asymptomatic, 3.0 (n = 7); urticarial reactions, 2.4 (n = 7); and with severe anaphylactic shock, 15–140 (n = 3). The assay used by these authors is, in my opinion, reliable. I doubt the validity of the assay system used by Atkins et al., inasmuch as incubation of their plasma samples with diamine oxidase reduced apparent histamine levels by 0 and 26% compared with a 64% reduction for plasma samples spiked with authentic histamine. Levels in all samples should have been reduced equally.

I did state in my editorial that "biologically active lipids such as prostaglandins, leukotrienes (SRS-A) and platelet activating factor (PAF) as well as chemotactic factors and hydrolytic enzymes are released along with histamine." I also pointed out that epinephrine is a useful antidote, "as it will abort the entire degranulation process" whereas the antihistamines do not ameliorate all symptoms of the allergic reaction. Few would disagree that the manifestations of immediate hypersensitivity reactions will depend upon the site of antigen entry. Degranulation of mast cells in small blood vessels following the intravenous injection of antigen will evoke a response quite different from that produced by degranulation of bronchial mast cells following inhalation of antigen. The disposition of the liberated substances and the distribution of receptors within individual tissues are also unknown and variable factors. The information we have is too limited and the system too complex to predict which mediator will be paramount in each circumstance, although there is little doubt that leukotrienes participate in airway smooth muscle contraction and histamine in episodes of tachycardia and hypotension. Irrespective of these uncertainties, an increase in plasma histamine levels is a sensitive and specific indicator of mast cell degranulation in vivo and is the best indicator we have to identify anaphylactoid reactions to anesthetic drugs.

In my view, the assessment of the role of the different mediators in anaphylactoid-type reaction must await additional clinical studies. Meanwhile, the studies initiated by Philbin et al. at the Massachusetts General Hospital have provided actual data which, hopefully, will stimulate further research in this area.

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REFERENCES

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Drug Toxicity Should Affect Drug Choice

To the Editor:—The important symposium report, "The Anesthesiology Triad in Obstetrics," concluded "all drugs are toxic if used improperly." Of course, but was that the real point of the symposium? Wasn't it that all drugs are not equally toxic and that it might sometimes make sense to choose a possibly less toxic drug?