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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 criticized 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.[1] 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.[2–5] We agree that our correlation[2] taken as an isolated report does not necessarily imply causation. However, when the effect on SVR can be prevented by histamine antagonists as we reported,[6] 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.[7] 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 ludicrous.

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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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,[1] 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,[2] who have carefully documented eight cases of drug-induced reactions associated with histamine release. My monograph[3] in-