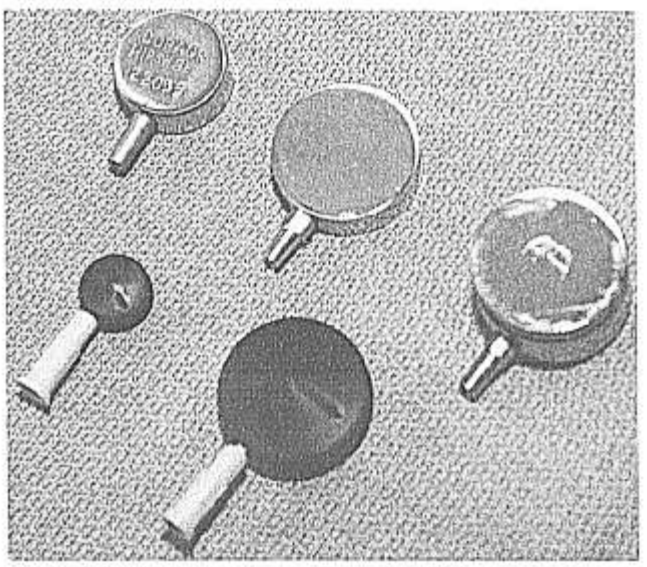

Fig. 2. Common pediatric- and neonate-sized precordial stethoscopes compared to precordial stethoscopes made from 6- and 50-ml syringes.

metal, it can be used in magnetic resonance imaging or computed tomography scans, for which pediatric patients frequently require monitored sedation or general anesthesia.

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Table 1. Precordial Statistics

	Outer Diameter (mm)	Weight (g)
Monoject syringe size (ml)		
3	9	0.5
6	13	0.7
12	17	1
20	21	1.7
60	26	4
Commercial precordial stethoscopes		
Martin-premie	22	11
Martin-light	25	11
Martin-infant	29	14
Wenger-child	29	79
Wenger-adult	38	184

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Subanesthetic Isoflurane and the Ventilatory Response to Hypoxemia

To the Editor:—Several years ago, I reported that 0.1 MAC isoflurane selectively impairs the ventilatory response to hypoxemia.[1] Recently, Temp *et al.* observed that 0.1 MAC isoflurane reduces this response when sustained hypoxemia is induced with hypercapnia but not when hypoxemia is induced with normocapnia.[2] They concluded that their "data indicate that 0.1 MAC levels of isoflurane do not affect the response to sustained normocapnic hypoxia."[2] In considering possible reasons for the disparate conclusions of their study and ours, Temp *et al.* overlook certain critical differences between the studies themselves.

Study Conditions. During testing, our subjects relaxed in a darkened and completely quiet room.[1] The subjects of Temp *et al.* were "required to watch a documentary videotape" and may have been aware of the sounds of circuit motors. In addition, while exposed to 0.1 MAC isoflurane, Temp *et al.*'s subjects were touched or spoken to periodically to prevent presumed complicating effects of sedation or changes in level of consciousness.[2] As Severinghaus has pointed out, *all* extraneous stimuli must be avoided when testing the response to hypoxemia because this particular response can be augmented falsely by even subtle stimuli—such as whispering by laboratory personnel.[3] Further, Temp *et al.*'s rationale for imposing such stimuli appears misplaced because anesthetic-induced sedation does not in itself necessarily depress the hypoxemic response[4] and, even if it were to do so, it would be inappropriate to attempt to neutralize this component of its action when characterizing the effect overall.

Size of Control Response. When moderate normocapnic hypoxemia was induced in our subjects in the control condition over a period of 8–10 min, ventilation increased to 18.1 ± 1.0 L/min (mean

± SE).[1] When the same level of hypoxemia was induced in Temp *et al.*'s subjects abruptly, ventilation peaked at 26.2 ± 3.8 L/min and then settled to 15.9 ± 1.2 L/min over the subsequent 20 min.[2] The control responses of our subjects were typical for the particular conditions to which they were exposed,[5-7] but those of Temp *et al.*'s subjects appear unusually large.[8-10] (In the only studies closely comparable to that of Temp *et al., i.e.,* with the *identical* level of hypoxemia induced over a similar time period, together with eucapnia and normal levels of resting ventilation, the peak hypoxemic ventilation was 19.9 ± 2.0 L/min[8] and the 20-min values 9.8 ± 0.4[9] and 9.9 ± 1.0 L/min,[10] means ± SE.)

The apparently augmented control responses of Temp *et al.*'s subjects may have been due to extraneous stimuli (as suggested above) and/or to behavioral influences on breathing. Such biased responses could obscure an effect of isoflurane on the chemoreflex response *per se.* They also would explain why Temp *et al.* detected an effect of isoflurane when hypoxemia was induced with hypercapnia but not with normocapnia, because the more intense chemical stimulation of hypercapnic hypoxemia would reduce the relative impact of extraneous factors.

Statistical Inference. The conclusion of our study rejects the null hypothesis with an indicated type I error $P < 0.05$.[1] The conclusion of Temp *et al.* accepts the null hypothesis, but without an estimate of power or the probability of a type II error.[2] Temp *et al.* present 95% confidence limits for the effects of isoflurane on the control response in their subjects and infer that these limits "clearly exclude" our mean findings.[2] Unfortunately, this inference may not be valid, because the mean control response of Temp *et al.*'s subjects was above the 95% confidence limits for the control responses of our volunteers. Further, the mean control values of hypoxemic ventilation in Temp *et al.*'s subjects, both the peak value and that at 20 min, are well beyond the 95% confidence limits tabulated for the corresponding values from the most comparable investigations.[8-10]

Thus, these two studies differed in several important ways. One, performed in quiescent conditions, found that a typical response to hypoxemia was impaired by 0.1 MAC isoflurane consistently and inferred this effect of isoflurane with reasonable statistical probability. The other, performed with confounding extraneous stimuli, found that an unusually large response was affected variably and concluded the absence of an effect (as above) without statistical evidence. However one wishes to interpret each of these differences, they should not be ignored.

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In Reply:—Knill suggests we have accepted a null hypothesis, a conclusion based upon one phrase of a sentence in the abstract. Readers who went beyond the abstract found:

> Thus, the major finding of the study is the inability to reproduce the large, dramatic reductions of the acute hypoxic ventilatory response previously reported with 0.1 MAC concentrations of inhalational agents. A small to moderate reduction, however, can not be excluded by the data.[1]

In fact, we observed no significant effect of isoflurane on the acute hypoxic response, whether induced with normocapnia or with hypercapnia. The reduction of the *sustained* hypoxic response with hypercapnia, to which Knill alludes, also was substantially less than the 50–80% reductions previously reported *for the acute response.*[2] We noted that the acute and sustained responses are mediated somewhat differently and that Knill *et al.* has studied only the acute response.[2]

We went on to point out that "it seems probable that [Knill *et al.*'s] isoflurane confidence limits would overlap ours in the area of a 20–30% reduction" for the acute response.[1] And the final sentence of the manuscript begins, "The difference between our results and