Jouppila *et al.*, 1978,[4] measured IBF after epidural anesthesia with 4 ml bupivacaine 0.5% in eight patients and with 4 ml bupivacaine 0.5% with epinephrine 5 μg/ml in 10 patients. The addition of epinephrine 20 μg produced no significant effect on IBF, although four of the patients who received epinephrine had decreases in IBF. Thus, 4 ml of local anesthetic solution containing epinephrine 5 μg/ml (compared with a 3-ml recommended test dose) would be unsafe by Dr. Marx's rationale. However, Jouppila *et al.*, 1978,[5] studied the effect on IBF of lumbar epidural anesthesia for cesarean section in nine patients administered 16–20 ml lidocaine 1.5% with epinephrine 5 μg/ml. There was a mean decrease of 13% from the control value that was not statistically significant. The largest decrease in IBF occurred in two patients with simultaneous arterial hypotension. The mean decrease in IBF in the other seven patients was 8 $ml \cdot 100\ g^{-1} \cdot min^{-1}$ (reproducibility of the technique is $\pm 20\ ml \cdot 100\ g^{-1} \cdot min^{-1}$).

There are no clinical studies that have demonstrated any adverse effects on the neonates of mothers who received local anesthetics epidurally that contained epinephrine 5 μg/ml. Conversely, there is a large clinical series of 1,946 patients who received large volume (20 to 25 ml) caudal anesthetics (mepivacaine = 748 patients; mepivacaine with epinephrine = 658 patients; and lidocaine with epinephrine, 515 patients) that had no differences in neonatal outcome between the three groups.[6]

Based on my knowledge of bupivacaine cardiotoxicity in obstetrics, I believe that epinephrine should be added to all doses of epidural bupivacaine where total incremental dosage exceeds 50 mg.

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In reply:—Dr. Albright's contention that epidural epinephrine can be used safely in obstetric practice is based primarily on three studies of intervillous blood flow (IVBF) undertaken at the same institution by a radioisotope method that limits the number of tests permitted.[1-3] Thus, according to the protocol, only one postepidural determination was performed, immediately after a uterine contraction and 10–15 min following the injection of the anesthetic. Epinephrine is a rapidly acting drug of limited duration so that its peak effect well may have subsided at the time of determination. Nonetheless, in only one of the three studies[1] did IVBF remain unchanged in all cases—following injection of bupivacaine 20 mg with epinephrine 20 μg, a dose that approximates that recommended as a test dose. In the second study,[2] 10 ml of local anesthetic containing 50 μg of epinephrine was administered to 12 parturients, and IVBF declined markedly in three of these. In one instance, this was explained as secondary to an unanticipated uterine contraction. In the other two cases, however, the fall was associated with a decline in maternal mean blood pressure to below 75 mmHg in the presence of a systolic pressure above 100 mmHg; the underlying severe decrease in diastolic pressure obviously points to an epinephrine-induced loss of vascular resistance. In the third study,[3] epinephrine 80–100 μg was added to 16–20 ml lidocaine in nine gravidae scheduled for elective cesarean section, and in seven of these, the subsequent decline in IVBF ranged from 4 to 58%. The mean decrease of 13% was "statistically" not significant, but the clinical importance was not ascertained as fetal ECG was not recorded.

In these investigations, epinephrine was used to prolong the action of the local anesthetic, not to rule out accidental intravascular injection. Despite its administration into the epidural space, decreases in IVBF were demonstrable in at least 18% of cases following addition of epinephrine

50 μg and in 78% following 80–100 μg. The effect of such doses injected directly into a blood vessel is conjectural for the human. However, continuous recordings in pregnant sheep have shown reductions in uterine blood flow of close to 60%, beginning 30 s after the intravascular injection of 20 μg of epinephrine and lasting longer than 3 min.[4] Even if transient decreases of this magnitude can be tolerated by a healthy fetus, they may be disastrous in the presence of an already compromised uteroplacental or umbilical cord blood flow. Furthermore, intravascular injection of epinephrine will cause maternal cardiovascular responses including potentially hazardous arrhythmias.

It is my considered opinion that proper testing procedures and fractionated injections of bupivacaine obviate the need for added epinephrine. However, for the anesthesiologist who is uncomfortable using bupivacaine without epinephrine but hesitates to administer two potentially cardiotoxic drugs (bupivacaine and epinephrine), there are three local anesthetics (2-chloroprocaine, lidocaine, and mepivacaine), none of which, according to FDA information, has ever been implicated directly in a fatal cardiac arrest in a parturient and can be employed safely without adding epinephrine.

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Is Nothing Certain with Small Sample Sizes?

To the Editor:—Two groups of authors in two recent studies[1,2] implied that the observations of zero events in seven and 13 patients, respectively, rule out any long-run risk of observing either of these events in the population. To many, a report of zero events in a sample of observations, irrespective of the sample size, suggests that observing such an event is extremely unlikely. This may not always be true.

In the first study,[1] Liu *et al.* found zero apneas in seven premature infants who had preanesthetic histories of apneas but now were greater than 46.7 weeks conceptual age. The authors did not discuss the possible postanesthetic risks of this older group of ex-premies. As a result, the authors implied that apneas do not occur in this older group. In their editorial,[3] Gregory and Steward state that "further prospective studies are needed to delineate those most at risk of having apnea develop." Nevertheless, this study will have a significant impact on our anesthetic practice. Can we be certain that, because zero cases of apneas were observed in the seven older ex-premies in Liu's study, the long-run risk of postanesthetic apneas in the entire population of ex-premies who are greater than 46.7 weeks conceptual age is zero?

In the second study,[2] LaMantia *et al.* investigated the course of 13 patients previously exposed to bleomycin who subsequently received a mean $F_{I_{O_2}}$ of 41%. They observed zero cases of respiratory failure in the 13 patients and concluded that "enriched inspired O_2 concentration was not hazardous in a testicular cancer population . . . the oxygen concentration administered to such patients . . . should not be curtailed." Whether or not bleomycin and an enriched oxygen concentration together cause respiratory failure is not at issue. What is at issue here is whether we can accept their conclusions that zero cases of respiratory failure in 13 patients rules out any long-run risk of observing this event in the entire population of bleomycin-treated patients?

Both of these studies imply that finding zero events in "n" observations means that the long-run risk of observing the event in the population is also zero. This is not true. In a recent review of this problem, Hanley and Lippman-Hand[4] applied an expression for predicting the maximum long-run risk (with 95% confidence) of observing an event when the event is not found in a sample size of "n" observations: Maximum Risk = $1 - \sqrt[n]{0.05}$. If "n" is greater than 30, then the expression for the Maximum