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In reply:—We appreciate Dr. Karis's interest in our recent letter. I believe he underestimates somewhat the amount of heat a humidifier can deliver, for he has forgotten that when gas fully saturated at 47°C cools in the respiratory tract, water condenses giving up the heat of vaporization. Five liters of gas fully saturated at 47°C contains 80/760 × 5,000 = 526 ml water vapor (P_{H_2O} at 47°C = 80 mmHg). When this gas is cooled to 37°C in a patient's respiratory tract, it will deliver 526 − 309 = 217 ml (0.159 g) of water as well as 92 calories from the condensation of the water. Compared to cold dry gas, the total calorie saving would be 264 cal/min at $\dot{V}_I$ of 5,000 ml. We would use a $\dot{V}_I$ of 7,000 ml in a 70-kg individual (dead-space gas must be included in heat calculations) and I therefore calculate the calorie saving from humidification to be 22,176 cal/h. Noback and Tinker[1] suggest that the drop in core temperature postbypass is due to a loss of heat from the "core" to other parts of the body which are insufficiently rewarmed. If we assume the "core" consists of the vessel rich group (9 per cent body weight) plus the total intravascular volume (7 per cent body weight), then we are delivering enough heat to prevent a 2°C/h drop in core temperature.

Mathematics aside, the technique works. Dr. Karis suggests we employ other more efficient measures but this is unlikely. We do use a warming blanket but have found as did Noback that it has little effect on core temperature. Our operating room is at 18°C and our patients are uncovered from chin to feet during the procedure. We still believe the technique is as safe in the adult population as it is in the pediatric age group and has proven effective not only in open heart patients but in those undergoing major intraabdominal procedures where heat loss is a problem.

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Nitrous Oxide As an Anti-stress Agent?

To the Editor:—The paper by Roizen *et al.* seems to highlight the possibility that the anti-stress effects of the anesthetic agents used may well have been partially mediated by the nitrous oxide (N_2O) used as the common anesthetic vehicle.[1]

It has been shown both *in vivo*[2,3] and *in vitro*,[4] that N_2O at analgesic doses is an opiate agonist. The concentration of N_2O used in the study falls within the limits which could be considered analgesic.

It has been shown experimentally that there is an inhibitory feedback mechanism mediated by the adrenergic and opiate system involving the locus coeruleus,[5] and arcuate nucleus of the hypothalamus,[6] respectively. The anti-stress effect reported here may have been caused by the activation of this feedback mechanism by an opiate agonist.

There is some experimental evidence in man that N_2O analgesia has anti-stress properties.[7,8] In addition, a number of conditions with a large stress component such as postoperative pain,[9] asthma,[10] and the alcoholic withdrawal state[11] have been successfully treated with N_2O analgesia.

The effectiveness of N_2O in postoperative pain control[9] may not only result from its analgesic effect, but also by diminishing the excessive response to stress.

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Pitfalls in Deriving Pharmacokinetic Variables. I

To The Editor:—The reports of Morgan *et al.*[1,2] and the editorial by Stanski[3] fail to emphasize several problems in deriving the rate of elimination of a drug from its plasma concentration *vs.* time curve.

One problem is that in analyzing the plasma concentration *vs.* time curve over several hours, it is not possible to distinguish between elimination or irreversible loss of the drug from the plasma, and distribution of the drug into tissues with especially long time constants. For instance, for thiopental assuming 75 per cent protein binding, 20 per cent of the body weight consisting of fat, a fat/blood partition coefficient of 11,[4] and 7 per cent of a 6 l/min cardiac output going to fat, the time constant for fat tissue would be approximately 22 hours. Ghoneim and van Hamme's[5] three-compartment model predicts that distribution will be complete in approximately 2.5 hours after the bolus administration. One may reasonably assume that after this time the distribution of thiopental into fat is not complete. In fact, it may not be complete at the end of their 12 hour data collection period; thus, the drug that goes to fat during this period appears to be irreversibly lost, that is, it appears to be excreted. A similar "overestimation" of the true elimination of other drugs used during anesthesia may be found if plasma levels of the parent drug can be determined for several days.

Another problem is that the model independent pharmacokinetic variables, clearance and apparent volume of distribution, are derived by integrating the plasma concentration *vs.* time curve from the time of drug administration to infinity. Obviously, the shorter the data collection period, the larger the possible error in the integration, and hence in these two variables.

Pharmacokinetic studies of drugs used during anesthesia in which data are collected for several hours are still quite useful to anesthesiologists because they do describe the amount of drug in the plasma, and presumably the rapidly equilibrating tissues during the course of the average anesthetic period. One must be aware that the shorter studies may overestimate the importance of drug elimination and underestimate the importance of drug distribution. Further studies are needed to attempt to correlate the variation in pharmacokinetic variables seen between individuals and variations in those factors which influence drug distribution such as cardiac output, degree of protein binding and regional blood flow.

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