Anesthesiology
51:487, 1979

Are Additional Cancer Studies Justified?

To the Editor:—Dr. Eger's excellent editorial on Dragons and Other Scientific Hazards[1] prompts me to write about a different but related dragon—the one that has to do with the alleged carcinogenicity of inhalational anesthetics in general, and isoflurane in particular.

I would like to state my opinion that the Commissioner of the Food and Drug Administration should not only stay, as has already been done, but in addition should also revoke the section of the regulations calling for teratogenicity and carcinogenicity studies of halothane, methoxyflurane, enflurane, and isoflurane. This opinion is based on several considerations. First, it is to be expected that fat-solvent inhalational anesthetics will alter the function of lipid membranes. That is the medical reason why they are administered. In addition to their desired effect on neural tissue, there will be undesired effects on other tissues. Embryonic tissue, if present, will be affected, as well as maternal tissue. This effect can be expected not only from inhalational anesthetics, but also from other fat solvents such as ethanol. Equieffective doses of various inhalational anesthetics seem to have about the same damaging effects on developing embryos. Extensive proposed studies would probably add little to what is already known.

Second, the alleged carcinogenic potential of isoflurane is based on its structural similarity to chloromethyl methyl ether, a known carcinogen.[2,3] However, their chemical activities are markedly different. Chloromethyl methyl ether is an active aklylating agent, and isoflurane is not.[4] The activity is the important factor, and the structure can only suggest the activity. How much money should be spent to prove the nonexistence of significant carcinogenicity from isoflurane?

Third, improper analogies have been adduced in the comparison of halothane, methoxyflurane, enflurane, and isoflurane with such compounds as vinyl chloride,[5,6] orally administered carbon tetrachloride, and orally administered trichloroethylene.[7] All of the latter group of compounds are extensively metabolized to compounds that are toxic.[8] Chloromethyl methyl ether, as previously mentioned, is an alkylating agent. Isoflurane, with which it has been inappropriately compared, is not; furthermore, it is less metabolized than any other inhalational anesthetic tested to date. In addition, data of questionable relevance have been generated by such practices as the oral feeding of trichloroethylene in large doses. The information gathered from the second group of compounds has little or no predictive value for the substances in the first group of compounds.

In conclusion, I believe that we should get rid of this dragon before it devours the emperor's new clothes.

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(Accepted for publication June 28, 1979.)

Anesthesiology
51:487–488, 1979

Minimizing Sore Throat

To the Editor:—I do not agree with some of the conclusions drawn from Loeser *et al.*[1] The statement that changes in cuff volume and pressure from nitrous oxide diffusion are similar in low-residual-volume, high-pressure cuffs as in high-residual-volume, low-pressure cuffs is, in my experience, only partly true.

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The intracuff pressure increases are similar in the two types of cuffs, but the volume increase is greater in the high-residual-volume than in the low-residual-volume cuff.[2] The increase in cuff-to-tracheal-wall pressure is equal to the increase in intracuff pressure in the high-residual-volume cuff. In the low-residual-volume cuff, however, it is very difficult to know how much the cuff-to-tracheal wall pressure will increase from an increase in intracuff pressure. I agree with Carroll that with high-residual-volume cuffs the increase in cuff-to-tracheal wall pressure is probably the main reason why postoperative sore throats occur more frequently when air is used to inflate the cuff during nitrous oxide–oxygen anesthesia.[3] I do not understand why the authors did not fill the cuffs with nitrous oxide, which is the logical consequence of the finding by Stanley.[4] This would have eliminated the problem of increasing cuff-to-tracheal-wall pressure during the period of intubation. In Uppsala we have used this technique for three years, with satisfactory results.

We have studied the effects of high-residual-volume and low-residual-volume cuffs on mucociliary clearance of the trachea in animal experiments. There is no doubt that high-residual-volume cuffs inflated to 20 cm H_2O pressure seldom arrest the transporation of mucus after extubation. On the other hand, we have found that the low-residual-volume cuff inflated to a slight leak during ventilation causes considerable arrest of mucus transport in the trachea even after only half an hour of intubation. Our experimental findings (unpublished observations), in contrast to the suggestion of Loeser *et al.*, indicate that high-residual-volume cuffs should be employed in clinical practice provided the cuff is filled with the same gas mixture as that used for anesthesia, and that the cuff pressure be measured.

Regarding the molded Lindholm tube, I regret to report that the tube used by Loeser *et al.* was obviously of the first experimental generation, which happened to have too short an intratracheal portion. In long-necked persons the cuff was therefore sometimes located in the larynx, which may explain why the incidence of severe sore throat was high with this model. Using molded Lindholm tubes with a longer intratracheal limb than the one used by Loeser *et al.* and low-residual-volume cuffs, we found an incidence of sore throat after intubation of 35 per cent, compared with 81 per cent following use of standard tubes (unpublished observations). Our mutual goal of developing tubes and techniques that are as non-injurious as possible would perhaps justify a multicenter investigation.

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(Accepted for publication June 29, 1979.)

Anesthesiology
51:488–489, 1979

In reply: — We appreciate the comments by Dr. Lindholm and find them quite rational. Indeed, a number of years ago we also believed that high-residual-volume, low-pressure cuffs should probably sustain greater volume increases than low-residual-volume, high-pressure cuffs when filled with air and exposed to nitrous oxide. We also suspected that the increase in cuff-to-tracheal-wall pressure secondary to nitrous oxide diffusion might be an important reason why postoperative sore throat occurred after endotracheal tube intubation. Unfortunately, our beliefs and suspicions, as well as those of Dr. Lindholm, did not stand up when subjected to careful scientific experiment. In a study in which 160 women undergoing similar operations had their tracheas intubated with five varieties of high-residual-volume, low-pressure air-filled cuffs and three varieties of similarly filled low-residual-volume, high-pressure cuffs (20 patients in each group) and were exposed to nitrous oxide and oxygen for similar intervals, there was no statistically significant correlation between initial cuff volume or pressure and changes in cuff volume or pressure during anesthesia, *i.e.*, changes in cuff volume and pressure were similar in low-residual-volume high-pressure cuffs and in high-residual-volume, low-pressure cuffs.[1] Some varieties of low-residual-volume, high-pressure cuffs, as well as some high-residual-volume, low-pressure cuffs, sustained larger increases

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