Correspondence

On Ethics in Human Experimentation

To the Editor:—I am writing in protest of the publication of the article "Intravenous Thiobarbiturate Anesthesia for Cesarean Section" by Kosaka, Takahashi, and Mark (ANESTHESIOLOGY 31: 489, 1969). By accepting any article for publication, the Editors give at least tacit approval to the ethical considerations involved as well as the scientific content embodied in the article. In the above instance I do not believe that the investigations meet present criteria for ethical human experimentation.

Any proposed investigations in humans must have positive answers to at least the following questions:

1) Is the investigation likely to provide *new* information?
2) Will such new information make a significant contribution to health care?
3) Is the experiment properly designed to allow adequate evaluation of the results?
4) What is the increased risk to the subjects and does the value of the information sought justify these risks?
5) Will "informed consent" be obtained from each subject?

The stated purpose of the above investigation was "to devise a method and define limits for safe use of intravenous anesthesia for cesarean section" (page 490). The method devised was to omit nitrous oxide from the well-established anesthetic routine of thiobarbiturate induction, nitrous oxide–oxygen and muscle relaxant for anesthesia for cesarean section. The safety of thiobarbiturate–N_2O anesthesia techniques for cesarean section was demonstrated more than 17 years ago[1] and has been confirmed repeatedly since then.[2-4] The pharmacodynamics of the thiobarbiturates and the muscle relaxants in pregnant and nonpregnant humans have been well established. No correlation has been established between maternal or fetal blood thiobarbiturate levels and fetal condition at birth, if the anesthetic technique is carried out within the already-established standards. It has been suggested that nitrous oxide is a desirable adjunct to prevent unpleasant recall of the surgery by the patient.[1] The only new information that might have come from this study would have related to the effectiveness of thiopental and oxygen alone in providing adequate maternal anesthesia. If the purpose was to define safe limits for a "new" technique, then the experiment should have been designed to obtain data which would allow the comparison of thiobarbiturate anesthesia with and without nitrous oxide. Did the investigators seek evidence of maternal recall during surgery, and, if so, why were the methodology and data not reported?

By the authors' own statements, the design appears to have been a non-design—"as the study evolved each patient was assigned to one of four categories" (page 490). Premedication was not controlled, nor were its possible effects evaluated, in the results. Patients in active labor and, therefore, presumably requiring emergency operation, were not differentiated from patients undergoing elective operation. (Artificial induction of labor prior to elective section can hardly be equated with emergency section for patients in active labor.) No mention is made of preoperative fetal condition in any of the patients. Thus, not only is the design inadequate, but so are the data as presented.

The risk normally associated with elective cesarean section was increased by the investigators by artificially inducing labor for the sole purpose of achieving "greater uniformity in the series"! Perhaps it will be argued that labor frequently is induced artificially for obstetrical or maternal convenience for normal vaginal delivery, and the investigative method, therefore, followed normal practices. If these patients were normal risks for labor and vaginal delivery, why were they scheduled for cesarean section? If they were not normal risks, how can one justify artificial induction of labor? How, in any case, can one justify in-

creasing the duration of anesthetic exposure and manipulation solely in order to obtain data on abnormally prolonged induction–delivery intervals? (page 492).

Finally, nowhere is it indicated to what extent, if any, the patients were informed of the contemplated studies, the risks to themselves, and their unborn infants, or whether consent to the studies was in fact obtained.

In view of the above considerations, I believe that the investigations were unnecessary in terms of the likelihood of developing new information, that any new information which might have been obtained would not have represented a significant contribution to health care, the studies were improperly designed and the results inadequately evaluated, and that it was unethical to subject the mothers and infants to the increased risks involved even if properly informed consent were obtained. I strongly urge that ANESTHESIOLOGY insist on compliance with ethical standards for human experimentation in all investigations accepted for publication.

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EDITOR'S NOTE

The Editorial Board has not found it easy to establish an all-inclusive policy regarding the publication of papers in which human experimentation is involved. As this matter has been aired, our task has been made easier by the investigator's assumption of the basic responsibility for proper conduct in this sphere. We, too, accept the responsibility. We are helped in our resolve to support the basic principles of ethics in human experimentation by letters such as that of Dr. Fletcher and that of Dr. Beecher, published in the March issue of the Journal.

The Bohr Equation

To the Editor:—In a recent article (ANESTHESIOLOGY 31: 575, 1969), Kuwabara and Duncalf have revised Enghoff's modification of the Bohr equation,

$$\frac{V_D}{V_T} = \frac{Pa_{CO_2} - P\bar{E}_{CO_2}}{Pa_{CO_2}}$$

to account for the fact that when the physiologic shunt is greater than 20%, the Pa_{CO_2} will be significantly different from Pc_{CO_2} to make the standard Bohr equation give a falsely high V_D/V_T.[1]

The final result,

$$V_D/V_T = \frac{\left(P\bar{v}_{CO_2} - \frac{P\bar{v}_{CO_2} - Pa_{CO_2}}{1 - \dot{Q}_s/\dot{Q}_t}\right) - P\bar{E}_{CO_2}}{P\bar{v}_{CO_2} - \frac{P\bar{v}_{CO_2} - Pa_{CO_2}}{1 - \dot{Q}_s/\dot{Q}_t}}$$

although mathematically correct, is cumbersome and difficult to commit to memory. To overcome these objections I present the following modification of their derivation. Starting with their same assumption:

$$Pa_{CO_2} = \dot{Q}_s/\dot{Q}_t P\bar{v}_{CO_2} + (1 - \dot{Q}_s/\dot{Q}_t)Pc_{CO_2} \quad (1)$$