



### *A Consideration of Control in Research*

Two separate investigations of the hemodynamic effects of diethyl ether on man are reported in this issue of ANESTHESIOLOGY.<sup>1,2</sup> These papers are of particular interest because of the acknowledged competence of the two reporting groups—Kubota and associates and Jones and associates.

In both reports the avowed or implied purpose is to discover the hemodynamic effects of ether in human beings who are in a “steady state” of anesthesia and who have been subjected to minimal preanesthetic medication and have not had the complication of surgical operations.

In both reports the authors acknowledge other efforts to make similar studies but observe that in these less well-controlled studies the emergence of interpretable data seems unlikely. The philosophic theme of these reports is much the same and can be expressed in a statement from one of the papers. “Needs for the future include more rigorous control of variables.”

The meaning of the word “control” in these applications, however, may be more subtle and varied than the present authors suggest. To explore this view let us compare four major hemodynamic variables measured by the two groups:

*Blood pressure:* The Kubota group reports no consistent change. The Jones group reports

a consistent blood pressure fall with ether anesthesia.

*Central venous pressure:* The Kubota group reports an increase. The Jones group reports no consistent change.

*Cardiac output:* The Kubota group reports inconsistent changes. The Jones group reports that the cardiac output most often increases but does not always. The latter say too that this variable tends to increase with time.

*Peripheral resistance:* The Kubota group reports inconsistent changes; some up, some down. The Jones group reports that the peripheral resistance is consistently reduced.

Now consider the measurements of the same variables reported by Johnson,<sup>3</sup> Fletcher and associates,<sup>4</sup> and Prime and Gray<sup>5</sup> in three often quoted and less purely controlled studies and compare them with those of the Kubota and the Jones group.

*Blood pressure:* Johnson and Prime and Gray reported that this is consistently depressed. Fletcher and co-workers reported equivocal changes early with consistent depression later. These findings are supported by the observations of the Jones group but not by those of the Kubota group.

*Central venous pressure:* Johnson and Fletcher and associates found this increased. Prime

and Gray made no report. Here the Jones group reports equivocal change while the Kubota group agrees with Johnson and the Fletcher group.

**Cardiac output:** Johnson and Prime and Gray found an increase early and a decrease later. The Fletcher group reported that the cardiac output mostly increased early, but decreased later. The Kubota group, however, reports no consistent change whereas the Jones group reports that the cardiac output is most often increased early and increased in every case later.

**Peripheral resistance:** Johnson observed a decrease. Fletcher's group found inconsistent changes, and Prime and Gray did not report. The Kubota group, however, reports inconsistent change, and the Jones group, a decrease in the peripheral resistance.

One does not easily see a pattern of consistency emerging because of the greater control achieved in these most recent attacks on this problem.

It is possible that over-rigorous attention to control by the attempt to remove influences foreign to the purposes of the study may introduce new and different extraneous forces as difficult to reckon as those abolished. The two reports under discussion may provide us with a specific example of such an instance. Although it must be acknowledged that the purposes of the two investigating groups were similar and their methods much the same, one (Jones and associates) was much more vigorous in eliminating premedicants as a foreign contributor to the findings.

Of all comparable data reported by the two groups, the only ones revealing a *startling difference* pertain to the concentration of ether in arterial blood at the times of hemodynamic observations. The analytic method used was the same in each study. The depth of anesthesia was in one study "EEG level 4" with conditions suitable for abdominal surgery, and in the other, light enough that spontaneous respiration maintained the carbon dioxide tension at less than 50 mm. of mercury. Yet, in the latter, the mean concentration of ether in the arterial blood was 129 mg. per 100 ml. while it was only 88.5 mg. in the former study. Beside this husky difference in the concentra-

tion of ether in arterial blood, the small differences in hemodynamic variables presented seem pale indeed.

One possible explanation of these findings may be developed as follows: Only 88.5 mg. of ether per 100 ml. of blood is needed to produce anesthesia if the subject is premedicated as were those in the Kubota group, but with more rigorous control as in the subjects in the Jones group, 129 mg. of ether is required. Therefore, the premedication contributed the equivalent of 40 mg. of ether per 100 ml. to the depth of anesthesia in subjects in the Kubota group.

Another explanation, perhaps just as defensible logically, can be made in this manner. Some factor such as the unsuppressed stimulus of anxiety during a prolonged period of anticipation suffered by the subjects of the Jones group during their initial control observations and manipulations may have produced hormonal, autonomic nervous, or other effects requiring large concentrations of ether for their abatement. When this extraneous factor (the unsuppressed stimulus of anxiety) was controlled by the modest premedication used by the Kubota group, much smaller concentrations of ether were required in the blood.

Thus it may be that those steps taken to exclude unwanted effects may prove to have a significant and unplanned influence on the values under observation.

In the conventional sense there is no question which of the two studies under review here is the better controlled. In a broader sense it would be difficult or impossible to say. It is apparent, however, that much more information is available to us because we have *both* of these excellent works to compare, and because they were done in different ways. Had they been equally well controlled, in the conventional sense, it is likely that they would have yielded less information.

Recognition of the importance of control in experimentation was certainly one of the great contributions to human progress, but its forms are varied and often subtle. There is still value in assembling careful observations of a phenomenon in its own habitat (say hemodynamics during ether anesthesia—as it is used during surgical operations). The value increases as the accompanying conditions are

defined. The value increases even more as the observations are compared with others made with somewhat different accompanying conditions also well defined. It may be said that this is also a form of control.

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### References

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## *The New England Journal of Medicine*

ONE hundred and fifty years ago, two Boston physicians, John Collins Warren and James Jackson, collaborated in publishing a weekly medical journal entitled, *The New England Journal of Medicine and Surgery and the Collateral Branches of Science*. Only a few years earlier, these same gentlemen had similarly joined in founding the Massachusetts General Hospital. Their efforts resulted in the formation of one of the renowned medical institutions of the world and a medical journal that has continued its weekly appearance until in 1962 it is celebrating its sesquicentennial, now under the style of *The New England Journal of Medicine*.<sup>o</sup> It may come as a surprise to many to learn that *The New England Journal* is the oldest regularly published weekly medical journal in the world. Some journals began appearing earlier, but due to lapses in publication, have lost claim to the title. *ANESTHESIOLOGY* is proud to salute *The New England Journal of Medicine* and its distinguished editor, Dr. Joseph Garland.

<sup>o</sup> The ancestral background:

- 1812—*The New England Journal of Medicine and Surgery and the Collateral Branches of Science*.
- 1827—*The New England Medical Review and Journal*.
- 1828—Combined with *The Intelligencer* to form *The Boston Medical and Surgical Journal*.
- 1828—*The New England Journal of Medicine*.

Perhaps more than any other speciality of medicine, Anesthesiology owes a particular debt to *The New England Journal* for it was in the pages of an ancestor that the first accounts appeared of the use of a general anesthetic for a surgical procedure in man. The November 18, 1846, issue of *The Boston Medical and Surgical Journal* contained an article entitled "Insensibility During Surgical Operations Produced by Inhalation," written by Dr. Henry J. Bigelow, a surgeon at the Massachusetts General Hospital. In this report, Dr. Bigelow gives an account of an operation performed on October 16, 1846, upon a patient anesthetized by Dr. Morton with the alleged intention of producing insensibility to pain. The operation, performed by Dr. Warren, was comparatively slight in extent and involved an incision near the lower jaw. During the operation, the patient muttered, as if in a semi-conscious state, and afterwards stated the pain was considerable, though mitigated. This was thought to be some defect in the process of inhalation. The next day, another patient inhaled the substance during the removal by Dr. Hayward of a fatty tumor of considerable size. The operation lasted four to five minutes, after which the patient said he had felt no pain even though he had portrayed occasional signs of uneasiness. Dr. Bigelow describes the use of the agent in four additional cases. One of these demonstrated excitement