

### Concerning Experimental Results

THIS ISSUE OF ANESTHESIOLOGY contains two excellent articles by Cristoforo and Brody dealing with the circulatory modifications which anesthetic agents can effect. Their findings differ importantly from those previously reported, including our own. It is my privilege to comment upon them. I view my function not primarily as that of a critic but as that of an historian who attempts to achieve some scenic harmony by providing a perspective.

It is always disquieting when one laboratory finds that it cannot confirm the work of another, although this happens far more frequently than is usually realized. There are at least three major causes for such an event: (1) the experimental subjects differ; (2) the experimental techniques differ; or (3) the interpretation of similar results differs. The first category is not uncommon, for there are certain marked alterations in response which are caused by species difference, diet, or environmental factors. The second cause is nearly always present; indeed, it is improbable that two investigators, even if they set out to perform the same experiment, would actually succeed in doing so. Most experiments have to be learned; the experimenter and his subjects interact in a way which is determined both by the personality of the former and the responses of the latter. This follows from the obvious, but somehow-overlooked, fact that the systems which a physiologist wishes to study are, quite simply, unavailable for study. In the vast majority of cases one cannot investigate a normal function without making it abnormal, or dead, and the experimental approach involves treating the problem like an opaque "black box" which can be observed only from without. The investigation of the box is built around the numbers and kinds of responses that it can be made to give . . . their consistency, and their interpretability. Out of these responses a theory is constructed concerning the way in which the box is "wired." Naturally, the inter-

pretations of various investigators depend in part on what they believe to be contained within the box, and thus we are introduced to item 3, above, which may be among the most important sources of disagreement.

The present authors have clearly demonstrated a vasoconstrictor action exerted directly by cyclopropane upon the vascular smooth muscle of the perfused dog gracilis muscle. In this they confirm an effect first described by us (Price and Price: ANESTHESIOLOGY 23: 16, 1962) in 1961 during a study of rabbit aortic strips. However, they did not find (as we did) that cyclopropane enhanced the response of the vascular smooth muscle to norepinephrine, nor could they find any evidence that cyclopropane administration increased sympathetic nervous activity. They concluded that the only important vascular influence of this anesthetic was due to its direct peripheral action.

Judged solely on the basis of the data which Cristoforo and Brody present, there is no other view which can be justified. On the other hand, there are many observations, and particularly those which have been made in man, which indicate that their conclusion is too sweeping. For example, cyclopropane administration caused an increase both in renal and in splanchnic vascular resistance, but this increase could be abolished by ganglionic blockade, and cyclopropane when given after a sympathectomy had been performed had little or no effect upon resistance (Miles *et al.*: J. Physiol. 118: 140, 1952; *ibid.*: Clin. Sci. 11: 74, 1952; Price *et al.*: ANESTHESIOLOGY 26: 312, 1965). The increase in skeletal muscular vascular resistance described by McArdle and Black (Brit. J. Anaesth. 35: 352, 1963) in patients receiving cyclopropane has not been a uniform finding (Cleaton, H.: to be published; Kitchin *et al.*: Clin. Sci. 12: 361, 1953; Abramson *et al.*: ANESTHESIOLOGY 2: 186, 1941) and there are some areas (*e.g.*,

cerebral circulation) where the direct actions of cyclopropane appear to be vasodilator (Wollman, H., to be published). This list of discrepancies could be multiplied several-fold; however, I believe that my point has been made. At the least it can be said that the dog gracilis preparation, as it was used, does not appear to be a reliable guide in the prediction or interpretation of human pharmacologic responses.

Reservations also apply to an analysis of sympathetic nervous reactivity based upon measurements which do not quantitatively or even uniquely reflect sympathetic nervous activity. Indeed, previous work (Deutsch *et al.*: J. Pharmacol. Exp. Ther. 135: 354, 1962) has indicated that, in the dog, the principal sympathetic response (to cyclopropane) is mediated via the adrenal medullae whose secretions were excluded from access to the blood perfusing the gracilis in the experiments described. The present results (lack of vasoconstriction), therefore, cannot demonstrate what the authors claim—a "failure . . . to demonstrate any significant activation . . . of the sympathetic nervous system . . ." (by cyclopropane). Here again a direct measurement of such activity would have been preferable, as would the use of a basal anesthetic other than pentobarbital (which appreciably reduces the response to the subsequent administration of cyclopropane).

An area of real confusion is related to our earlier suggestion (ANESTHESIOLOGY 24: 1, 1963) that cyclopropane might depress medullary depressor neurons to an extraordinary degree. In the first place, the medullary "vasomotor center" is thought to contain only two major types of neurons (pressor and depressor) and to be inhibited only through baroreceptor activation of the depressor cells (which have no spontaneous activity). Because of this the mere observation of peripheral vascular tone or of its modification by various reflexes tells one little or nothing concerning which part of the medullary mechanism is affected. In fact, reflex depressor and pressor responses are believed to represent respectively the activation and deactivation of one and the same barostatic mechanism; therefore, differences in the two responses can only

result from peripheral actions and the present authors' interpretations appear unjustifiable. Our efforts to get at this problem were two: (1) discrete electrical stimulation of pressor and depressor areas within the medulla, and (2) localized injections of saline equilibrated with cyclopropane, both series of observations leading to similar results. Since then there has been only one valid attempt to pursue the problem—that of Markee *et al.* in 1966 (ANESTHESIOLOGY 27: 742, 1966). These authors used a somewhat different technique than we did, adopted considerably different criteria, and concluded exactly the opposite of what we had. Unfortunately, a clear test of our hypothesis, by direct observation of the threshold for excitation in individual medullary neurons, is so formidable technically that it has never been attempted.

The action attributed to halothane—that of causing vasoconstriction by the release of antidiuretic hormone (ADH)—is novel and of considerable interest. While it has been known for years that many anesthetic drugs cause antidiuresis (presumably because they cause ADH secretion) it has not been considered likely that they would liberate enough ADH to cause circulatory changes because the ratio of pressor to antidiuretic threshold doses is of the order of 1,000 to 1. Of course, the direct answer to this question would have been to make measurements of circulating ADH. Unfortunately, simple and adequate methods have not yet been developed (although difficult analytical methods now exist) and most arguments are still being based upon indirect evidence, as the present paper is.

Like most imaginative work, this effort raises more questions than it answers, and it is here that I would like to dilate upon the pitfalls of extrapolation. The preparation used is a very special one, as the authors recognize. Would cat gracilis behave the same?—or human quadriceps? And, if it is true that significant ADH liberation occurs during halothane anesthesia in man, why doesn't total and regional vascular resistance increase? The observations of Deutsch (ANESTHESIOLOGY 27: 793, 1966) suggest that ADH liberation during halothane anesthesia in man is insufficient to affect the renal vascular resistance and, although some

groups have noted an increase in total systemic resistance, a larger number has not. It is permissible to wonder why ADH liberation (or any other proposed mechanism) varies so much among different groups of subjects. Or do the important variations reside instead among the investigators and their individual approaches? In any case, it is clear that successful model testing in a population as complex as a group of living organisms requires a degree of experimental reproducibility which may exist only in our dreams. None of this is meant to impugn the present authors' findings; it is meant instead to examine the distance over which they can safely be extrapolated. One can only impatiently await the day when all of the substances which circulate in human blood and which have cardiovascular actions (e.g., ACTH, bradykinin, angiotensin, prostaglandin, oxytocin, serotonin, kinetard) and many of which are found in high concentrations in the brain can be measured easily and specifically. When that time comes the questions posed by these experiments should be explicitly answerable.

It is clear that if I had no aim in writing other than to criticize no useful purpose would be served. I would rather emphasize again the point that biology has its own "uncertainty principle" in that one cannot examine life processes without destroying, or at least changing, them. It is for this reason that crucial experiments cannot, in general, be performed in man. Ideally, one would like a "preparation" consisting of a free-moving, conscious, intact, perfectly normal animal (with human responses) from which the desired information was broadcast automatically; the receiver, of course, would have an infinite signal-to-noise ratio! In reality, the experiments which biologists perform are more or less ingenious ways of probing living systems from without. The measurements are indirect, the control exercised over these systems is small and the room for disagreement is extraordinarily large. Paradoxically, the best controlled and most powerful experiments are often those

whose interpretation in terms of normal physiology is most uncertain. This follows naturally from the fact that precision and controllability are actually gained only at the expense of destroying those normal integrative mechanisms which account for the delicately poised attitude and for the perpetual spontaneous variations which characterize viable systems. As only one example, we now know that several generations of biochemists were entirely misled concerning the actions of insulin because they were studying cell-free systems. The standard preparation was quite controllable and the results reproducible, but they had little to do with the *in vivo* actions of insulin which largely reflect its ability to alter membrane permeability.

One has only to think for a moment of the distortions introduced by the experimental system itself to recognize how abnormal the "control" situation often is. For example, we anesthetize a dog with a barbiturate, place it in a position which it may never assume naturally, paralyze it, permit its temperature to vary, heparinize it, operate upon it with unsterile instruments, ventilate its lungs artificially and give a number of vasoactive drugs in moderate to large dosage. After this we give another anesthetic by inhalation and expect that the response will not have been modified by anything we have done previously! Again, this analysis is not directed specifically at the present contributions. But, if we are to understand human pharmacology, it is well to be appropriately cautious in interpreting the results of any acute experiments performed in lower animals. The present controversy can be encompassed with the observation that the systems under study are enormously more complicated, intricate, and sophisticated than are the present experimental methods for dealing with them.

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