Of Dogs and Men

Everyone who knows medical students is familiar with the old complaint—usually voiced by second year students, "but I want to learn about 'people,' not about dogs, and cats, and mice, and..." The complaint is not serious, and it soon dissipates. Eventually, they hear about man and even the most ardent "people" students realize that much can be learned from animals that is applicable to man.

However, much that is to be learned cannot be discerned in animals. Concerning the action of drugs, in particular, the ultimate information must come from man. There is often, but not always, a species difference in the action of drugs. There are pathological conditions that cannot be reproduced and, of course, there are external factors which may influence drug action and which are impossible or very difficult to produce in animals. Thus we must study drug action in man.

But there are limitations to studies in man. If we wish to analyze a drug's action, we have to do so by "taking the system apart," reducing step by step the complexity of intact man or animal. Drug effects in the intact mammalian organism are almost never the result of selective drug action, almost always complicated by the operation of secondary, usually compensatory, mechanisms. Thus if we choose to analyze them, we must simplify the system: restrict drug distribution, use blocking or antagonistic agents to eliminate one or several of the multiple drug actions, or block compensatory secondary mechanisms. Finally, we may use isolated organs or even cell fractions to study drug actions in a simpler system. We can do this only to a limited extent in man.

The present issue contains the second article by List and Gravenstein on the pharmacological effects of scopolamine and atropine in normal man. As the authors have pointed out, this work is long overdue. It is surprising how incomplete our information often is concerning the effects of some of the "old standby's." Newer drugs are investigated more thoroughly because of their timeliness and because of the interest of the manufacturer. But often our knowledge concerning the older drugs presents gaps, gaps that seriously impair the clinical usefulness of these drugs. It is therefore gratifying that List and Gravenstein have provided us with more data on the effect of the commonly-used parasympatholytic agents. However, their study also points up the difficulties involved in the attempt to unravel the sites and mechanisms of action of these agents. Heart rate in the intact organism is the result of at least three factors: (1) parasympathetic, i.e., vagal, activity, (2) sympathetic, cardiovascular, activity, and (3) the magnitude of vagolytic action of the dose of atropine or scopolamine administered. It is very difficult, if not impossible, to separate these several factors in intact man. Thus the conclusions of the investigators must remain tentative. In animals, we can separate the various factors clearly: we can test the magnitude and the time course of the vagolytic effect by testing the response of the heart rate to electrical stimulation of the peripheral end of the severed vagus nerve. We can eliminate the influence of changes in sympathetic activity surgically, or by pharmacologically blocking sympathetic cardiovascular activity (spinal block, in-
hilitation of sympathetic transmission with reserpin or guanethidine, or blockade of the sympathetic receptor structures with a beta-adrenergic blocking agent). However, these experiments would have to be carried out under general anesthesia since psychic influence are not easily eliminated in unanesthetized, even well-trained animals, and psychic stimuli markedly affect heart rate in most laboratory animals.

Thus the final appraisal of the mechanism of the changes in heart rate following administration of atropine or scopolamine in man would have to be based upon experiments in animals and observations in man. Each set of observations has deficiencies—utilization of anesthesia in animals, incomplete separation of the complex interacting factors in man; but by intelligent and judicious interpretation of results obtained in both types of observations, the best possible estimate of the effect in man should be obtained.

While a complete analysis of mechanism and site of action of drugs can be achieved only by recourse to animal experimentation, the second purpose of drug studies of the type presented by List and Gravenstein is the collection of accurate and quantitative data in man. This is a goal that has been neglected much too long. It is a distressing situation indeed that the clinical use of almost all of our drugs rests upon a slim foundation of quantitative data concerning dose-response relationships. Even reference sources, such as the United States Pharmacopeia or New and Nonofficial Drugs, give no more than the "usual dose" for any drug. It is about time that this situation were remedied. There should be accurate data on dose response relationships in man obtained under clearly defined conditions. We are interested not only in the mean effective dose, or the average effect of a given dose, and the distribution of effects or doses as indicated by standard deviation or standard error, but we also need to know the extremes of the effects that might be encountered. For the purpose of comparing the potencies of two drugs in the laboratory, the mean potencies and the characterization of the distribution are sufficient since the interest is only in the average response of the population.

In the clinic, we would like to know any response which could possibly be encountered in the individual patient. Thus we should also know the extreme (maximal or minimal) effect of a given dose that might be expected, as well as the probability that such an effect might be seen in a given population.

The gathering of such data is a laborious task, and often it will not be the most exciting work: but it is work that has to be done. The observation of changes in heart rate after administration of parasympatholytics furnishes a satisfactory model for this type of investigation because the parameter to be observed is easily measured, and the factors involved in the physiological regulation of heart rate are fairly well understood. With many other drugs and other functions the situation is much more complicated, but, eventually, the same kind of studies should be carried out for all drugs.

We are interested not only in the magnitude of the drug effect, in the average as well as extremes, of a "normal" population, but we would like to reduce variability by defining different patient populations, distinguished by factors such as age, genetic make-up, and the presence or absence of pathological conditions. We would also like to know the influence of identifiable temporary factors upon the drug effect. Two questions will illustrate the point. What is the influence of reduction in sympathetic cardioaccelerator tone such as results from the administration of reserpine or any other drug which impairs impulses transmission in the sympathetic nervous system? And, what is the influence of environmental conditions upon the effect of the drug? As every physician knows, the usual sedative effect of scopolamine is sometimes supplanted by a stimulant or excitatory effect. Clinical observation suggests that the difference is related to the presence or absence of pain, but more accurate information would be of great value for the physician who has to decide whether or not to use scopolamine. It is conceivable that factors such as anxiety, fear, or the presence or absence of external stimuli, psychic as well as sensory, are able to influence the type of central effect produced by the drug. Although observations of this kind can be made in animals, they can be accomplished more
easily in man and the results would be more directly applicable to the clinical situation.

It should be obvious that much benefit can be derived from the closest cooperation between the "animal" and the "people" investigators. There is no inherent advantage or disadvantage to either method of investigation. There are merely different questions, and each has to be answered by the most appropriate means. Our understanding of drug action in the complex human organism requires both avenues of investigational approach.

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The Uptake of Ethylene in Man

A wealth of information on anesthetic uptake and distribution in man has been published in the last several years. Though seemingly of recent origin, much credit for developments in this field must be extended to earlier investigators, most particularly to Howard W. Haggard and Seymour S. Kety. Haggard, in 1924, was the first to measure anesthetic uptake (diethyl ether) in the dog and to relate his results to predicted values.\textsuperscript{1, 2, 3} Although his techniques of measurement and theoretical description of ether uptake were somewhat naive by present standards, Haggard clearly recognized the direct relation existing between anesthetic uptake and anesthetic solubility, pulmonary ventilation and cardiac output. Kety, in 1951, refined the uptake theories of Haggard and others, and offered a mathematical description of uptake for all inert gases that, as a first approximation, is still valid.\textsuperscript{4, 5} Of greater significance, however, was Kety's recognition that anesthetic uptake in pulmonary capillary blood is important only as it affects the rate at which alveolar anesthetic concentration rises toward the inspired concentration. It is this rate of change in alveolar concentration that determines in large part how rapidly anesthesia may be induced or recovery achieved.

Severinghaus, in 1954, published the first detailed measurement of uptake of an inhalational anesthetic (nitrous oxide) in man.\textsuperscript{6} Although nitrous oxide uptake roughly approximated Kety's predicted curve, there was sufficient deviation between the actual and predicted curve to suggest that the Kety theory contained a basic error. Similar deviations appeared in subsequent experimental determinations of rate of rise of halothane\textsuperscript{7} and cyclopropane\textsuperscript{8} alveolar concentrations in man. One error was acknowledged by Kety himself. For mathematical simplicity, he had assumed that cardiac output was distributed uniformly throughout the body, although the importance of differential distribution of blood on uptake had been suspected long before.\textsuperscript{9} Experimental evidence suggests instead that 70 to 80 per cent of the cardiac output in man is distributed to a small body volume (approximately 6 to 10 per cent of the total body mass), consisting of brain, heart, kidney and splanchnic bed, while the remaining 20 to 30 per cent of cardiac output goes to muscle, skin and fat, comprising up to 80 per cent of body volume. The remaining 10–20 per cent of the body volume is made up of bone, ligaments and tendons. Because of their extremely small blood supply, these tissues play no appreciable role in uptake. Theoretical uptake curves obtained from electrical\textsuperscript{10, 11, 12} or mathematical\textsuperscript{13} models, which permit adjustment for differences in distribution of blood flow to various body compartments or tissue groups almost mirror experimentally determined uptake curves of ether,\textsuperscript{14, 15} halothane,\textsuperscript{16, 17} methoxyflurane\textsuperscript{18} and fluroxene\textsuperscript{19} obtained in man. Likewise, rates of rise of alveolar concentration of nitrous oxide\textsuperscript{20} and fluroxene\textsuperscript{19} are nearly identical to predicted curves.

In this issue of Anesthesiology, Salanitre, Rackow, Wolf and Epstein report their work on ethylene, the least soluble of the commonly used anesthetic gases. They measured the rate of rise in alveolar ethylene concentration over a 30-minute period in 8 subjects and found at least 95 per cent equilibration with inspired concentration in all subjects in the first 5 minutes (fig. 1, in their paper). Further, they found that the mean alveolar concentration curve for 8 subjects was in close agreement with predicted values (fig. 2, same paper). Despite apparent closeness of the predicted