membership will exert their rights and privileges. One frequently hears the comment, "The Society is run by a small group of members." Yet those making such comment are many times not willing to participate actively in working out the problems which such an organization must face. In 1959, as well as in the future, only active participation of every member both at a local and national level can assure progress of our specialty in an effective and democratic way.

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On Species Differences

THE never-ending search for better therapeutic agents taxes the ingenuity and the patience of the pharmacologist, who must screen innumerable compounds to find the few potentially useful ones. His preliminary appraisal of these proposed new drugs is based entirely upon the results of experimentation in laboratory animals, results which cannot be transferred indiscriminately to man. For example, observation of the excitatory action of morphine in the cat might lead to an entirely erroneous prediction of the response to morphine in man. The same drug given intravenously in a dose of 1 mg./kg. provides adequate preanesthetic sedation in the dog, but in a 70 kg. man this dose would be disastrous.

Most instances of species differences in drug effects are quantitative rather than qualitative. Hexobarbital (Evipal) produces sleep in laboratory animals, but the duration depends upon the species. Given 100 mg./kg., mice awaken in a few minutes, rabbits sleep nearly an hour, rats longer still, and dogs sleep for many hours. Brodie (J. Pharm. & Pharmacol. 8: 1, 1956) has demonstrated that this difference in sleeping time is related to variations from one species to another in the rate of inactivation of hexobarbital by the enzyme systems present in liver microsomes. The mouse metabolizes hexobarbital rapidly and soon awakens; the dog inactivates the drug very slowly and sleeps for a long time. Which of these findings may one reasonably apply to man? It is apparent that only studies with human subjects can furnish the desired answer.

Man is the ultimate experimental animal. He is also the most complex. Hypotheses concerning mechanism of drug action derived from appropriate studies in animals must be verified (or disproved) in man, applying the same rigorous standards of research to human subjects in the clinic as to other animal species in the laboratory. Indeed, even greater skills may be required to design, conduct and evaluate safe studies in man than in animal investigation. Above all, great care must be exercised to avoid injury in human studies.

In clinical trials of new drugs, quality, not quantity is essential;

numbers alone can be dangerously misleading. An uncritical observer, influenced by favorable reports from the animal laboratory, may reach overly optimistic conclusions about the efficacy of a new drug in man, conclusions seemingly substantiated in large numbers of patients. With suitable experimental design, reliable measurements and adequate controls, the discerning worker would have been able to recognize the shortcomings of the drug early in the study. In other words, the numbers themselves, large or small, are blameless, provided the methodology is strict in design. Indeed, large series may then be highly informative.

The most recent demonstration of the pitfalls because of failure to appreciate species differences concerns the so-called ultrashort acting barbiturate methitural (Neraval). Careful work by Blake and Perlman (J. Pharmacol. & Exper. Therap. **117**: 287, 1956) showed that in dogs and rats methitural is localized in fat and metabolized by the liver considerably more rapidly than is thiopental. Unfortunately these findings do not carry over to man, despite enthusiastic claims to the contrary based upon early clinical trials. Gale (ANESTHESIOLOGY **18**: 573 1957) collected quantitative data showing that in man there is no important difference between methitural and other thiobarbiturates in clinical use. The ideal intravenous anesthetic remains to be found.

The postman, the peddler and the pharmacologist have learned to heed the warning, "*cave canem.*" The anesthesiologist can profit by their example.

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TWELFTH POSTGRADUATE ASSEMBLY

New York State Society of Anesthesiologists, Inc.

December 10–13, 1958

Hotel New Yorker, New York

Scientific Sessions	Clinics at Various Hospitals
December 10 and 12	December 11

Residents Program—December 13