Title: THE CASE FOR DESIGNER ANIMALS:
USE OF SIMULATION TO REDUCE ANIMAL STUDIES

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**INTRODUCTION:** The gap between what a drug or device is designed to do and its actual effect in clinical practice is responsible for much of the added cost and slow acceptance of new medical technology. Adequate testing in spite of physiological differences and changing test situations requires that relatively large numbers of subjects be studied in clinical and animal trials. To decrease the use of animals, as well as to save time and money, we have begun to substitute a computer model for the subject.

**METHODS:** A blood pressure controller that adjusts the infusion of sodium nitroprusside (SNP) to create and respond to changes in mean arterial pressure (MAP) was tested by using it to control pressure in three classes of experimental subjects: A) live anesthetized dogs; B) a computer model of the drug's dose-response characteristics[1]; and C) a more complete computer model of the cardiovascular system[2] and the action of SNP including the baroreceptor response[3] anesthetic effects and individual physiologic variation. An experimental protocol consisting of step changes in set point, as well as perturbations: wrong drug concentrations, arterial catheter flushes, a disconnected infusion catheter, and pharmacologically induced severe hyper and hypotension was performed on each class of subject. Perturbations were produced in the live subjects by manipulation and in virtual subjects by simulating the manipulations. In the live dogs, MAP was obtained from a femoral artery cannula inserted percutaneously and a Hewlett-Packard Model 1290A pressure transducer. SNP was infused with a McGaw/Accupro infusion pump controlled by a digital computer. The computer monitored the arterial pressure and continuously adjusted the pump infusion rate to maintain desired mean pressures. The virtual subjects (computer models) were sent the infusion rate and produced mean arterial pressures which were read by the monitoring software.

**RESULTS:** Simulation allowed us to reduce animal experimentation by 82.5% over three years, cutting our animal studies from a projected 120 to 21. Each animal study produced two hours of protocol data in 3-4 hours of real time and required an additional 4-8 hours to setup and 4-6 hours to shut down. A complete simulated two hour study took 40 minutes (using the complex model) or 15 minutes (using the simple model). Simulation thus reduced the time for a typical study by 94% (from 11 hours to 40 minutes). The animal studies produced more information than the simulations since the behavior of the animals was more complex than that of the models. When the animals were inconsistent in their responses (varying by as much as 70% to sequential infusions of identical drug doses) we found it difficult to tell in vivo whether changes were due to our device modifications or to changes in the animal.

**DISCUSSION:** The simulation models were quite useful in solving the problems suggested by the animal experiments. They certainly decreased the use of animals. The simulations also provided several advantages that would have been impossible with live animals:

1) Studies were reproducible on exactly the same (virtual) dog. Old experiments could be re-run for comparison with new studies after device changes. Multiple studies did not have to be performed to prove that a measured change in performance was real rather than a population or individual fluctuation.

2) Conditions or physiological quirks that were difficult to reproduce in live experiments or that were unusual in clinical practice could be modelled and repeated by simulation.

3) Circumstances that were dangerous to the subject could be simulated and the controller's response measured without danger to the subject and without the need to sacrifice animals.

4) Experiments could be performed whenever an individual was ready to run a test without waiting for a team to be assembled and without fear that procedural errors would invalidate the test data.

Although extremely useful, the simulations could not replace animal experimentation completely. The models were too simple to produce all the complex behavior seen in a typical live experiment and they could not uncover problems that they were not designed to simulate. The actual dose-response behavior of the drug and animal was found from live studies and the live studies provided a constant supply of new problems. We believe that the best use of resources involves a cycle in which animal experiments define problems which are then simulated and solved before additional animal studies are performed.

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