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1981

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Recommended Citation

Rowan, A.N. (1981). Regulation of biomedical research. *International Journal for the Study of Animal Problems*, 2(5), 227-229.

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Regulation of Biomedical Research

Andrew N. Rowan

The idea of abolishing or simplifying government regulations has a large following in Washington at the moment. As Reagan and his minions start to prune the growth of the past twenty years, we must hope that they are able to distinguish between the healthy growth which provides needed support and the unnecessary growth which strangles necessary initiatives. However, there is one area where we need more regulation rather than less, namely, biomedical research. In calling for more regulation in biomedical research, I do not mean the imposition of outside controls by allegedly ignorant and insensitive bureaucrats (although I think some outside control is unfortunately necessary), but rather the control which scientists themselves are meant to exercise over their work. I am calling for more attention to the regulation and control of experimental variables, such control being ever more important as the questions asked probe deeper and deeper into the subtle workings of biological systems.

In the 1940s, several researchers investigated environmental factors affecting various pharmacological parameters. Chen and colleagues (1943) demonstrated that the potency of insulin increased 40-fold from 20°-40°C, while the variance (square of the standard deviation) dropped over 4000-fold. Chance (1947) showed that the toxicity of an amphetamine varied according to the number of mice housed together, the toxicity for ten mice housed together being one tenth that for solitary animals. Others have followed the example set by these studies and have attempted to assess the effects of various environmental and stress-producing factors and their possible consequences for research (See *News and Review*).

In metabolic biochemistry, a warning was sounded by a group of German scientists for those who use *in vivo* metabolite levels to study regulatory mechanisms (Faupel *et al.*, 1972). In an elegant study, the metabolite levels of rat liver were measured using the standard "freeze-clamping" technique in which tissue is frozen to -193°C virtually instantaneously by clamping between aluminum plates which are pre-cooled in liquid nitrogen. However, with this technique, there is either an appreciable delay (greater than 10 seconds) in removing tissue from the killed animal, or the animal is anesthetized so that the tissue can be frozen *in situ* before the animal is killed. The possible effects of the delay, killing methods or anesthesia are usually ignored because of the problems of control. Faupel and his colleagues, using a simple double guillotine and rats that were in an unstressed state, showed that anesthetics, stress and violent killing techniques caused important variation in the levels of certain critical metabolites, such as adenosine monophosphate. By doing so, they called into question a great deal of earlier work and sounded a warning for anyone not taking these factors into account. Yet their study either is perceived to be an interesting curiosity or is ignored. The extra care which would be required is more than most researchers are willing to entertain, and they would probably argue that such extra control is not a requisite for the success of their particular research.

According to a recent article in *Science* 80 (December, 1980), the circadian rhythm is also very important, as an animal's response to a particular stimulant or drug treatment varies in a regular manner according to the time of day. For example, an LD50 dose of phenobarbital will kill no rats at the most favorable period during the day, but all will die if dosed during the least favorable period. Chronobiologists (those studying the consequences of diurnal and other regular biological rhythms) now argue that the results of some previous drug and cancer research studies are dubious; that many toxicology studies, especially of behavioral toxicity, need to be redone and that the conduct of scientific research must include controls for these time-dependent changes in all future studies.

The issue of stress effects has already been mentioned with regard to the study by Faupel and his colleagues. However, there are many such studies and there are probably few researchers who do not recognize that stress can adversely affect experimental results. Dr. W. Isaac (University of Georgia) discussed this issue at the 1979 annual conference of the American Association for Laboratory Animal Science, but argued that "we have not been concerned with behavioral variables, even though we give it a great deal of lip service and write regulations dealing with behavioral variables." He noted that there is little reinforcement for studies on the effects of environmental variables and no real commitment to attempt to control for them. A recent study on the response of rats to the stress of handling (moving the cages about) reports that a wide variety of metabolic and endocrinological parameters were markedly affected (Gärtner *et al.*, 1980). The authors note that "experimental or sampling procedures must be performed within 11 seconds of first touching the animals' cage." This is important for most of the endocrine characteristics and for all plasma values which are linked with circulatory change, capillary permeability, energy and mineral metabolism, and acid-base balance. If the experimenter is unable to perform the procedures quickly enough, "he must explain in detail how the stress due to manipulation influences the characteristics being studied." (*Emphasis added.*)

While this may be interesting, and the possible implications for results from past research disturbing, what does it have to do with animal welfare? Opponents of animal research commonly charge that experiments are repeated endlessly, while scientists argue that one must check the results of other research. But it is clear that a large amount of research is done without adequate control of the variables described above. This means that much of it may have to be repeated merely to control for the proper variables. While it may not be legitimate for animal welfare advocates to call for an end to all duplication of animal research, it is certainly legitimate for them to demand that scientists consider proposed research protocols far more carefully and that they take into account the factors mentioned above. Too many scientists follow, either wholly or in part, the dictum "Why think when one can experiment?" Such an approach is neither good economics nor good science. It has absolutely nothing to do with academic freedom, only with academic license.

Some would argue that the peer review system will prevent poorly planned research from being funded. But this is not necessarily true since the peers reviewing the research proposals are, by definition, guilty of the same omissions. Why should they pick up on a fault which they do not recognize in their own research? Of course, there will be some research projects which need not be concerned about environmental or chronobiological factors, but animal researchers should argue why they do not need to control for such variables, rather than the reverse.

The above proposals to take these additional variables into account will, no doubt, be perceived by many as irksome and unnecessary, but anyone interested in both promoting good science and preventing unnecessary repetition of animal research should demand such increased control. Blind empiricism should be forced out of biomedical laboratories, and we should instead strive toward the sort of research that was undertaken by Charles Nicolle, the French bacteriologist (Zinsser, 1940):

Nicolle did relatively few and simple experiments, but every time he did one, it was the result of long hours of intellectual incubation, during which all possible variants had been considered and were allowed for in the final tests. Then he went straight to the point, without wasted motion. That was the method of Pasteur, as it has been of all the really great men of our call-

ing, whose simple, conclusive experiments are a joy to those able to appreciate them.

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Is Nature Our Birthright?

Nancy Heneson

On December 2, 1980, former President Jimmy Carter signed into law the Alaska National Interest Lands Conservation Act, which will protect 104 million acres of federal land in Alaska (although mineral surveys will be allowed on protected areas where there may be oil and gas). In the words of former Interior Secretary Cecil Andrus (*DOI News Release*, 2 December 1980): "This law is the culmination of a nine-year national effort to protect the awesome wonders of our largest state as a part of a great legacy of beauty and nature that is the birthright of every American."

Webster's Third New International Dictionary (1976) defines "birthright" as a "right, privilege or possession to which a person is entitled by birth (as an estate or as civil liberty guaranteed under a constitution)." Leaving aside in this case the fact that dictionary definitions are often inadequate conveyors of a word's subtler connotations, the use of the legalistic term "birthright" in connection with beauty and nature reified as land bears closer examination, not only for its lexical peculiarity, but in its role as the linguistic vessel for transmission of a long-cherished idea. The concept of nature as something to which we (especially Americans) have a right, something that is our "legacy" or our "national heritage," manifests itself in the arguments of both developers and conservationists, hunters and trappers and animal protectionists. It has been used to justify manipulation, exploitation and destruction of life as well as to bolster efforts to establish parks, wilderness preserves and wildlife refuges. That such contrary attitudes toward the land and all of its inhabitants should be rooted in some of the same ideological soil is neither surprising nor illogical when one considers that the idea of rights, privileges and possessions presupposes the idea of ownership; ownership implies power, and power can be wielded either to the subjective benefit or detriment of the parties involved, including in this case that which is owned. Whether ownership adopts the philosophy of ruthless exploitation, benevolent stewardship, or some tortuously reached compromise between the two, follows from and is secondary to the deeply-ingrained idea that nature *belongs* to the human species.

By virtue of the Alaska Lands Act, some land in Alaska now belongs to the federal government, some to the state and some to native Alaskans. If someone, anyone, native Alaskan subsistence hunter, oil developer, or Washington environmental