ILAR Journal V35(1) 1993 [FORMERLY ILAR NEWS]
Models of Type I Diabetes - Part One

Letters

More on IACUCs and Merit Review

To the Editor:

A recent article in *ILAR News* [Prentice et al. 34 (1-2):15, 1992] examines the rationale for institutional merit review of research involving live animals. In my view, although the citations are probably appropriate, the authors' analysis leading to the main conclusion that there is an institutional responsibility for review of scientific merit, over and above a justified concern for parsimonious and humane use of animals, is incorrect on several grounds.

1. Prentice et al. equate the phrase "relevance to human and animal health" with "acceptable level of scientific merit." This is simply not the case. "Relevance" implies that the outcome of the research, positive or negative, will have some impact on human or animal health, while "merit" is a much more ephemeral issue that may or may not include a test for relevance within its context. Much fundamental research is seen to have relevance only long after it is completed, or it may take on relevance in a manner much different from original intentions. Furthermore, equation of human and of animal health by inclusion in a single phrase accepts as de facto the inappropriate assertions made by PETA [People for the Ethical Treatment of Animalsi and other organizations of the equivalence, and in some cases the primacy, of ethical obligations to animals over those to humans. This is a not generally acceptable minority viewpoint.

2. It is well established that merit review depends upon review by a principal investigator's peers. On a national level, peer review by a funding agency or a journal is made possible by reaching out to other investigators across the country and occasionally in other countries. Within any one institution, certainly there are individuals who can judge proposed research at the "fundamental level," but equally there are usually not those who can make peer judgements at the "knowledge-based level" (Prentice et al.'s terms). Imposing the need for external reviewers in internal decisions would increase delay and cost of research considerably, while reducing its timeliness and eventual relevance.

3. There is a profound difference in the consequences of external and internal review of research. The external review (by agency or journal) may result in a lack of funding or refusal to publish results. However, the investigator is free to pursue alternate funding and/or publication sources and ultimately, to perform the research as planned. Internally, especially in the context of review by the IACUC, a negative review effectively prevents the research from being conducted. Furthermore, despite the positive "spin" that Prentice et al. attempt to place on the interaction between the investigator and the internal review committee (IACUC or other), that interaction has a distinctly negative aspect; since the

investigator is reacting to the review process by altering the proposed research, his/her autonomy is clearly being limited. While Prentice et al. refer to "academic freedom" in the second paragraph of their discussion, they show a remarkable insensitivity to the real meaning of the phrase. External peer review groups, such as NIH study sections, take great pains not to plan or redirect proposed research when reviewing its merit, admissibility and fundability. Concern for noninterference with individual academic autonomy (freedom) should be viewed as even more important within the principal investigator's own institution, since the investigator and the institutional reviewers are colleagues.

Finally, on a related subject, while I certainly agree with Prentice et al. that an ethical "cost-benefit" calculation must be made in research involving either animals or humans, I must disagree very strongly that, in the latter case, the IRB [Internal Review Board] affects such a calculation by transferring "the decision-making responsibility to human subjects" and, by implication, transferring the ethical responsibility. In either case, the ethical responsibility resides with the principal investigator and remains there, whatever the advice of the IACUC or the IRB, respectively, may be. Consent must be sought from patients out of proper (ethical) respect for their humanity and autonomy. However, ethical responsibility is an *individual* attribute of the "doer" rather than of the "done to" and no consent and/or corporate decision, however well considered or rationalized, can alter the situation. We can enjoin individuals to act responsibly and punish lack of ethical behavior after the fact, but we cannot dictate the metes and bounds of such behavior prospectively. Recognition and assumption of individual moral responsibility is a distinguishing feature of mature, well-socialized human beings. Thus, there is an almost exact parallelism in this aspect of animal and of human research; the ethical "buck" begins and stops with the principal investigator.

I welcome Prentice et al.'s thoughtful discussion but suggest that they re-examine their conclusions in the light of individual academic freedom and ethical responsibility.

Sincerely,

Jonathan Black, Ph.D.
College of Engineering, Department of Bioengineering Clemson University
Clemson, South Carolina

To The Editor:

We wholeheartedly agree with Dr. Black's statement that "much fundamental research is seen to have relevance only long after it is completed or it may take on relevance in a manner much different from original intentions." As has been shown many times, it is not unusual for significant scientific discoveries to be serendipitous in nature. However, we wish to point out that assessment of a research project's relevance in advance of the completion of the research represents only a judgement that the proposed hypothesis to

be tested appears to have *potential* relevance. As we suggest in our paper, the term "relevance" in biomedical research means the research has potential value to human or animal health, the advancement of knowledge, or the good of society. Indeed, a statement of the importance of proposed experiments with respect to "health relevance" is specifically requested in the PHS 398 grant application. Relevance is obviously one of the key characteristics of scientific merit, along with a sound experimental design. If a research proposal has potential relevance or value *and* the experimental design is sound, we would contend that the research has scientific merit. It should, therefore, be conducted providing the ethical cost-benefit is acceptable and funding is available.

Dr. Black takes exception to the inclusion of the terms "human or animal health" in the same phrase and suggests this implies an equivalence "and in some cases the primacy of ethical obligations to animals over those to humans." We dispute Black's interpretation and strongly disagree with his contention that use of the phrase in any way "accepts as de facto the inappropriate assertions made by PETA" and other equivalent organizations. The phrase to which Black refers is part of Principle 1I of the U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training that were developed by the Interagency Research Animal Committee and implemented by the PHS Policy (PHS, 1986). Certainly, the framers of the PHS Policy, in response to the Health Research Extension Act (42 USC 289d) and amended Animal Welfare Act (7 USC 2131-2157) never intended to imply any equivalence between humans and animals. We suggest the phrase in question reflects the fact that legitimate animal research can be designed to benefit animals alone without any direct relevance to human beings. Clearly, veterinary projects that may result in animal health benefits should be an active area of research.

Dr. Black expresses concern that "imposing the need for external reviewers in internal decisions would increase delay and cost of research considerably, while reducing its timeliness and eventual relevance." Whereas we do not understand how an external review can possibly reduce the eventual relevance of research, we do agree that over reliance by IACUCs on external reviews would have a negative impact on research. However, as we indicated in our paper, protocols at our institution have rarely required outside review. Indeed, the few external reviews sought by our 1ACUC have been delivered in a timely fashion and have not prevented grant applications from meeting funding agency deadlines. In addition, the PHS Policy specifically authorizes such reviews in recognition that IACUCs may not have the prerequisite scientific expertise in all fields of research.

Perhaps the most disturbing aspect of Dr. Black's letter is his concern for preservation of academic freedom or, as he states, "noninterference with individual academic autonomy (freedom)." Black apparently considers the use of animals in research to be an academic right as opposed to a privilege that is granted by society. Freedom, be it academic or other, does not imply license under any guarantee of the constitution. Given the current threat to animal research and the concern expressed by the general public over the need to ensure appropriate animal welfare in this nation's research laboratories, we find Black's attitude to be both alarming and remarkably naive. The public, which overwhelmingly

supports valuable animal research that is humanely conducted, demands accountability. Quite simply put, investigators can no longer operate in relative autonomy in an environment devoid of any comprehensive system of checks and balances. Indeed, as we point out in our paper, the local institution now bears the ultimate legal responsibility for the research conducted within its walls. It is not in compliance with the PHS Policy for an IACUC to give approval for a protocol conditional upon successful peer review by the NIH because the committee cannot make a judgement regarding scientific merit. More importantly, Black fails to acknowledge that many research projects are initiated with in-house funds and, therefore, do not receive peer review at any grant agency level. Internally funded projects conducted without appropriate review can place the institution in a precarious position. It takes only one well-publicized research project labeled as unjustified to significantly damage the reputation of the institution and compromise the credibility of biomedical research in general. Therefore, if IACUC review implies interference with individual academic autonomy, it clearly does so with federal and public support. As we have learned, painfully, in the area of scientific misconduct, it is far better for science to police itself than have some external agency perform this function.

Dr. Black characterizes IACUC review that results in alteration of a proposed research project as being "distinctly negative." Apparently, he either does not understand or does not agree with the provisions of the PHS Policy. The Congress has the power to make whatever laws are consistent with the constitution, and it is Congress that has decided that animal research must be regulated and monitored by the PHS and the USDA. And, it is these organizations that have decided that the IACUC must serve that role at the institutional level. According to the PHS Policy, the institution through its IACUC has a legal obligation to assess the experimental design of a research project in order to ensure its soundness, while at the same time minimizing potential pain, discomfort, and distress the animals may experience and the number of animals to be utilized. Certainly, any IACUC review that takes into consideration the aforementioned criteria may, indeed, alter the proposed research after appropriate consultation with the investigator. However, what Black fails to recognize is that any alterations that may result will improve the research from an ethical standpoint without compromising its scientific validity. As a matter of fact, a properly performed IACUC review can enhance the probability of a research proposal being funded. Impetus for the alteration of research also occurs in the NIH review process. Contrary to Black's assertion that "NIH study sections take great pains not to plan or redirect proposed research," in reality, many investigators have found themselves involved in revision and resubmission of a proposal *until* the study section finds it acceptable.

Finally, we wish to comment on Dr. Black's last point regarding a transference by implication of the ethical responsibility for human subjects research to the human participants. In our paper, we specifically linked the transference of responsibility to the informed consent process. While an IRB must conclude that a given research project has a favorable risk-benefit relationship, the board, nevertheless, has the luxury of knowing that any prospective subject who finds the risk-benefit relationship of research participation unacceptable may simply choose not to participate. Anyone who has served

on a medical IRB realizes that in an ethically complex and/ or risky therapeutic experiment, respect for the patient's autonomy may become the overriding factor in determining the approvability of the research. We do not think our paper implied either directly or indirectly that investigators are not responsible for the ethical conduct of their research. Most assuredly, as Black points out, the ethical "buck" does begin and stop with the investigator. However, we wish to add that both the IRB and the IACUC serve to help researchers prospectively delineate their moral responsibility to human and animal subjects, respectively. Both the IRB and the IACUC are regulatory bodies empowered by the federal government and appointed by the institution. While Black implies that the advice of these review committees can be effectively disregarded, since "the ethical responsibility resides with the principal investigator," we can most assuredly state that the PHS, USDA, and FDA would strongly disagree with this characterization, implied or otherwise, of IRB/ IACUC authority.

We thank Dr. Black for his thoughtful review of our article, and while we disagree with many of his points, we are grateful for the opportunity to exchange ideas and opinions. The IACUC, in its present form, has been in existence only 7 years. As IACUCs and investigators continue to work together, we are confident that consensus will be reached and our privilege to continue to use animals in justifiable research will be better protected.

Sincerely,

Ernest D. Prentice, Ph.D.
David A. Crouse, Ph.D.
Michael D. Mann, Ph.D.
University of Nebraska Medical Center
Omaha, Nebraska

REFERENCE

PHS (Public Health Service). 1986. U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training. Pp 27-28 in Public Health Service Policy on Humane Care and Use of Laboratory Animals. Washington, D.C.: U.S. Department of Health and Human Services. (Available from Office for Protection from Research Risks, Building 31, Room 5B59, National Institutes of Health, Bethesda, MD 20892.)