Evaluation of Awarded Grant Applications Involving Animal Experimentation

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Evaluation of Awarded Grant Applications Involving Animal Experimentation

By Michael W. Fox, M. Andrea Ward and Andrew N. Rowan
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Washington, D.C.

And
Barbara Jaffe
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Institute for the Study of Animal Problems

The Institute was established as a scientific organization to explore and investigate the various relationships between man and animal. As the logo on the cover depicts, the Institute is concerned with the care, treatment and husbandry of laboratory animals, companion animals, farm animals and wild animals, all of which are bridged by the legal and moral aspects of animal rights. The Institute carries out research programs in these areas and is developing an information resource of pertinent references in the field of animal welfare science. The Institute disseminates relevant information through technical reports, monographs and a bi-monthly Bulletin containing news, comment, book reviews and reports of scientific meetings.

Additional information may be obtained by writing to The Institute for the Study of Animal Problems, 2100 L Street NW, Washington, DC 20037, (202) 452-1148.

INTRODUCTION

Forty years ago, there were few formal arrangements for setting social priorities for research or for regulating research activities and most of the funding for basic research came from private sources. As a result, the public was not particularly concerned with the way in which research monies were being spent. The limited federal funding was concentrated mainly on public health problems and on dietary deficiency diseases.

After World War II, the biomedical research program grew rapidly from $0.7 million in 1945 to $2.8 billion in 1974-1975. The growth, strongly supported by the public, could in part be attributed to the successes of the war research effort and the development of the new "wonder drugs". However, the situation began to change in the mid-1960's when research priorities began to be scrutinized more closely. More complex questions were being asked about the nature of the research and whether the use of animals in a particular program was justified by the proposed potential benefits.

The potential benefits of animal research are accepted by most. However, painstaking care must be applied to the approach and design of the research to ensure the best possible chance of achieving the research objectives and to minimize both physical and psychological distress to the animals. Consideration should be given not only to transport and housing conditions, but also to practices used in the laboratory. Adequate reasons must also be given as to why the research is necessary.

Public concern over the use and care of laboratory animals in biomedical programs contributed to the passage of the Animal Welfare Act in 1966 and its subsequent amendments. The Animal Welfare Act stated, inter alia, that research facilities should meet certain standards for the care and treatment of laboratory animals. The standards include minimum specifications for food and water, cages and enclosures, sanitation, temperature range, separation of species, veterinary care and euthanasia. The Act also states that reports should be filed on the number of animals used in painful experiments, with or without drugs to alleviate pain.

Recent books and articles have described abuses of laboratory animals. Painful Experiments on Animals (Pratt, 1976) lists a number of experiments conducted in New York which do not comply with conditions set by the Animal Welfare Act. Richard Ryder (1975) in Victims of Science and
Peter Singer (1975) in *Animal Liberation* have described experiments which raise serious ethical questions. The American Museum of Natural History in New York provides a recent example of both public and scientific concern (Wade, 1976) when the Museum's 15-year study on human hyper- and hypo-sexuality using cats as the experimental model was criticized for its repetitiveness and lack of relevance.

However, the use of laboratory animals is likely to continue for the foreseeable future and, therefore, scientists, veterinarians and animal care technicians have obligations to the animals to treat them humanely and to use them thoughtfully (i.e., sparingly, only as an absolute necessity when there are no other alternatives available, and even then, only when their use reasonably promises to contribute to the ultimate good of mankind or of other animals).

The ethics of biomedical experimentation on non-human animals and their "rights" are being explored today by many sectors of society (Morris and Fox, 1978), including research scientists and veterinary and medical doctors. We are on the threshold of an applied science of animal welfare and the scientific community can do much to foster advances in this field. Organizations already involved include the American Association for Accreditation of Laboratory Animal Care (AALAC), the American Association for Laboratory Animal Science (AALAS) and the Institute for Laboratory Animal Resources (ILAR).

It is increasingly being recognized by the scientific community that proper care and treatment of laboratory animals is essential for good research. Modern research is complex and exacting and attention to detail is necessary if the results are to be worthwhile. Fox (1979) has observed that "Scientists realize that no valid research can be conducted on sick or stressed animals (unless such variables are deliberately introduced and controlled) and that the animal's welfare is vital for good research. Bad animal facilities mean bad research or at least questionable conclusions which might be invalidated by (or contradict) similar studies conducted upon physically and psychologically normal animals." This same view has been expressed by Festing (1977) of the Laboratory Animals Center in the United Kingdom.

As a result of the growing and expressed concern of the public and the scientific community, the Institute for the Study of Animal Problems conducted a survey with the assistance of Technassociates, Inc. to establish, as far as possible, the extent to which relevant issues concerning animal use and care are being addressed in grant applications.

**OBJECTIVES**

The objectives of the study were:

1. To evaluate awarded grant applications to determine if research investigators had considered:
   a. The use of the most appropriate research model;
   b. The subsequent care for the model.

2. To compare changes (if any) in the above considerations which had occurred between 1972 and 1976.

3. To develop guidelines (if necessary) which could be used:
   a. When drafting a research proposal or grant application;
   b. When planning an experiment involving laboratory vertebrates;
   c. In evaluation of grant applications by peer review committees.

**METHODS**

The survey was based on reviews of selected, funded grant applications requiring experimental models and whole animal subjects for two selected years, 1972 and 1976. The identification of the approved and funded grant applications which used vertebrates as research subjects was accomplished by computerized searches completed by Scientific Program Analysis and Retrieval System (SPARS) and the Smithsonian Scientific Information Exchange (SSIE).

Four agencies were selected for the review. These were the National Institutes of Mental Health (NIMH), the National Institute for Alcoholism and Alcohol Abuse (NIAAA), the National Institute for Drug Abuse (NIDA) and the National Science Foundation (NSF). NSF was selected in order to have one funding agency outside the NIH orbit and, therefore, not subject to the same degree of government control. All of the agencies fund a substantial portion of research involving animals and a reasonable sample of grant applications could be selected for each year and from each agency.
The searches identified 959 suitable grant applications from the four agencies. Table I shows the number of grants selected together with the total number of grants awarded by each agency in 1972 and 1976.

<table>
<thead>
<tr>
<th>Agency</th>
<th>Total Grants*</th>
<th>New Grants in 1972</th>
<th>Number of New Grants Selected for Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIAAA</td>
<td>132</td>
<td>51</td>
<td>32</td>
</tr>
<tr>
<td>NIDA</td>
<td>185</td>
<td>94</td>
<td>55</td>
</tr>
<tr>
<td>NIMH</td>
<td>1884</td>
<td>702</td>
<td>153</td>
</tr>
<tr>
<td>NSF**</td>
<td>2265</td>
<td>1630</td>
<td>144</td>
</tr>
</tbody>
</table>

*Training grants were not included. The breakdown of the total grants figure changed between 1972 and 1976 and, therefore, a comparison is not possible. The figures in the table are provided as a rough guide only.

**The numbers refer only to grants made by the Biological and Behavioral Sciences Division. The new grants figure includes all those grants which have come up for renewal after three years. (The total number of grants for all divisions of NSF in 1972 and 1976 were 5658 and 7007, respectively.)

***N.A. Suitable breakdown not given and, therefore, the training grants could not be extracted from the totals provided by the agencies.

The applications were reviewed (see Appendix A) with the aid of a questionnaire (see Appendices B and C) consisting of 47 questions (with subdivisions) which were used to form four broad categories of concern. These are: a) Validity of Animal Modeling Approach; b) Efficiency of Animal Use; c) Quality of Methodology; and d) Minimizing Stress/Adequacy of Facility.

Validity of Animal Modeling Approach

The concept of the animal model and the use of a research animal has become so widely accepted in designing a new project that alternative approaches may not be considered. Researchers generally study animals in order to answer questions about the functioning of the human body in health and disease and, in some cases, may overlook the obvious—namely, that the problem could be solved (or at least investigated) by studying man directly. In addition, there may be an in vitro alternative which could perform the same task as well, if not better than the animal system. Applications were assessed to determine the extent to which such questions were explicitly considered.

Efficiency of Animal Use

The selection and availability of the appropriate animal model for the study are important considerations. Factors such as strain, source and status of the animal should have been considered as well as the question of sequential use of animals. In addition, the investigator should have considered what is the least number of animals required to produce a statistically significant result and the problem of reducing the number of unwanted variables. Applications were assessed to determine animal resource utilization.

Quality of Methodology

The objectives of the research should be clearly stated and a description of data analysis and step-by-step methodology provided. Applications were assessed to determine whether or not there was evidence of a thorough literature search and a justification of the present project in relation to prior research work in the field.

Minimizing Stress/Adequacy of Facility

The Guide for the Care and Use of Laboratory Animals (ILAR, 1978) as well as other relevant literature on care and
treatment of laboratory animals should be consulted prior to preparation of grant applications. Applications were assessed for details of proposed cage sizes, dietary requirements, animal care personnel, restraint devices and other points mentioned in the questionnaire as well as the adequacy of the support facilities available in the animal facility, especially the presence of adequate surgical facilities and expertise where necessary.

There were four possible answers to each question—Yes, No, Blank (indicating insufficient information to make a judgement), and Not Applicable. For the purposes of the final analysis, a blank answer was judged to be negative. The veracity of the information provided in the application was not checked by the analyst and a mere passing comment or indication that a particular point had been considered was sufficient to elicit a positive response from the reviewer.

Answers to each question were summarized into the four categories and expressed as the ratio of favorable responses to the total applicable responses, converted to percentage form.

RESULTS

The reader should be aware that a negative response in the questionnaire does not indicate that an applicant did not consider a particular question. The issue may have been raised but not thought to be appropriate for inclusion in the final grant proposal. Also, some questions may have been considered the responsibility of the institution's support staff and not of the individual investigator.

The questionnaire provided a rigorous examination of the extent to which grant applications address issues relevant to the use and care of laboratory animals. Many of the points in the questionnaire should have been answered when applying for funds from the NIH according to their guidelines issued in 1971. However, only a relatively small proportion of the questions achieved a positive score of more than 50% (Table II). Those that reach the 50% mark are related mainly to the justification of the animal modeling approach and to major methodological issues. However, very few applicants addressed the issue of the number of animals required for the proposed studies, the procedures for minimizing stress, and housing facilities. There were many blank or not applicable responses and these have been discussed in more detail in Appendix D.

The percentage change in positive responses between 1972 and 1976 for four selected questions is shown in Table III. Substantial differences exist between the agencies but it is not clear why these should occur. The NSF applications generally addressed more of the issues than those submitted to the NIH agencies.

Table IV shows the percentage of positive responses in each of the four categories for applications funded in 1972 and 1976. While Table IV demonstrates that there may have been some improvement between 1972 and 1976 regarding the most appropriate animal model and the subsequent care for that model, the differences are not statistically significant. Very few applications gave details relating to Stress/Facilities for the experimental animals, the highest figure for the two years being 19%. However, the percentage of positive responses for all four categories either rose or remained static, the largest increase being in the NIMH "Validity" category where the level of positive responses rose by 19%. Table IVa, providing a measure of dispersion of the figures, is given in Appendix E.
TABLE II
Total Responses for the Four Agencies to the Questionnaire for 1976

<table>
<thead>
<tr>
<th>Question</th>
<th>% Yes/Applicable Response</th>
<th>Actual number of total responses of all four agencies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td><strong>Animal Modeling Approach</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A 1. Is the use of animal-model approach argued?</td>
<td>74</td>
<td>414</td>
</tr>
<tr>
<td>2. Is the possibility of &quot;alternatives&quot; explored?</td>
<td>68</td>
<td>198</td>
</tr>
<tr>
<td>3. Is the applicability (in human terms) of the work argued?</td>
<td>42</td>
<td>231</td>
</tr>
<tr>
<td><strong>Efficiency of Animal Use</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B 1. If the experiment repeats earlier work, is repetition argued?</td>
<td>84</td>
<td>310</td>
</tr>
<tr>
<td>2. Is the model chosen as representing the most accurate simulation?</td>
<td>69</td>
<td>394</td>
</tr>
<tr>
<td>3. Is choice of species (strain, breed) argued in terms of least cost to environment and least stress?</td>
<td>55</td>
<td>314</td>
</tr>
<tr>
<td>4. Is the number of animals required argued?</td>
<td>3</td>
<td>18</td>
</tr>
<tr>
<td>5. Is source of animals named?</td>
<td>40</td>
<td>230</td>
</tr>
<tr>
<td>6. Is the possibility of sequential use (after another experiment) raised?</td>
<td>8</td>
<td>35</td>
</tr>
<tr>
<td>7a. Are genetic variables minimized?</td>
<td>18</td>
<td>90</td>
</tr>
<tr>
<td>b. Are protocols given for prescreening for uniform experimental stock?</td>
<td>14</td>
<td>67</td>
</tr>
<tr>
<td>8. Is the possibility of sequential use (after this experiment) raised?</td>
<td>12</td>
<td>35</td>
</tr>
<tr>
<td><strong>Quality of Methodology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C 1a. Evidence of literature research for prior work?</td>
<td>99</td>
<td>572</td>
</tr>
<tr>
<td>b. Evidence of literature research for statistical methodology?</td>
<td>19</td>
<td>106</td>
</tr>
<tr>
<td>c. Evidence of literature research for animal models?</td>
<td>46</td>
<td>256</td>
</tr>
<tr>
<td>2. Is necessity of research in view of earlier work argued?</td>
<td>92</td>
<td>526</td>
</tr>
<tr>
<td>3. Are the objectives of the research stated?</td>
<td>99</td>
<td>567</td>
</tr>
<tr>
<td>4. Is methodology for interpretation and analysis of data given?</td>
<td>29</td>
<td>169</td>
</tr>
<tr>
<td>5. Is step-wise experimental methodology described?</td>
<td>90</td>
<td>517</td>
</tr>
<tr>
<td>6. Is methodological description given for animal on experimental table?</td>
<td>62</td>
<td>311</td>
</tr>
<tr>
<td><strong>Minimizing Stress/Adequacy of Facility</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D 1. Evidence of literature research for animal housing and care?</td>
<td>5</td>
<td>25</td>
</tr>
<tr>
<td>2. Does housing conform to ILAR space guidelines?</td>
<td>13</td>
<td>58</td>
</tr>
</tbody>
</table>
### Question

3a. Are there adequate facilities for sterilizing equipment?
3b. Are there adequate facilities for experimental procedures?
3c. Are there adequate storage facilities for food and supplies for animals?
3d. Are there adequate sanitation facilities?
3e. Are there adequate facilities for waste disposal?
3f. Are there adequate facilities for screening outside contaminants?

### Applicable Response

<table>
<thead>
<tr>
<th>Question</th>
<th>% Yes/No</th>
<th>Actual number of total responses of all four agencies</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a. Are there adequate facilities for sterilizing equipment?</td>
<td>18</td>
<td>94 419 1 61</td>
</tr>
<tr>
<td>3b. Are there adequate facilities for experimental procedures?</td>
<td>52</td>
<td>273 250 1 51</td>
</tr>
<tr>
<td>3c. Are there adequate storage facilities for food and supplies for animals?</td>
<td>14</td>
<td>65 391 1 118</td>
</tr>
<tr>
<td>3d. Are there adequate sanitation facilities?</td>
<td>11</td>
<td>53 444 1 77</td>
</tr>
<tr>
<td>3e. Are there adequate facilities for waste disposal?</td>
<td>3</td>
<td>13 473 1 88</td>
</tr>
<tr>
<td>3f. Are there adequate facilities for screening outside contaminants?</td>
<td>5</td>
<td>24 441 1 109</td>
</tr>
</tbody>
</table>

4. Are animal's dietary requirements considered?
5. Is number of animals/cages argued?
6. Are exercise needs considered?
7. Is isolation housing argued?
8. Are veterinary services continually available?
9. Is noise control considered?
10. Is need for restraint devices argued?
11. Is the need for tagging devices argued?
12. Is training of animal care personnel considered?
13. Is separation of non-compatible animals considered?
14. Are laboratory personnel instructed in least stressful procedures?

<table>
<thead>
<tr>
<th>Question</th>
<th>% Yes/No</th>
<th>Actual number of total responses of all four agencies</th>
</tr>
</thead>
<tbody>
<tr>
<td>4. Are animal's dietary requirements considered?</td>
<td>23</td>
<td>104 351 1 119</td>
</tr>
<tr>
<td>5. Is number of animals/cages argued?</td>
<td>23</td>
<td>104 355 1 115</td>
</tr>
<tr>
<td>6. Are exercise needs considered?</td>
<td>9</td>
<td>41 403 3 128</td>
</tr>
<tr>
<td>7. Is isolation housing argued?</td>
<td>2</td>
<td>10 136 299 130</td>
</tr>
<tr>
<td>8. Are veterinary services continually available?</td>
<td>19</td>
<td>88 373 4 110</td>
</tr>
<tr>
<td>9. Is noise control considered?</td>
<td>13</td>
<td>58 393 1 123</td>
</tr>
<tr>
<td>10. Is need for restraint devices argued?</td>
<td>3</td>
<td>15 126 308 126</td>
</tr>
<tr>
<td>11. Is the need for tagging devices argued?</td>
<td>1</td>
<td>7 46 420 102</td>
</tr>
<tr>
<td>12. Is training of animal care personnel considered?</td>
<td>18</td>
<td>84 378 3 110</td>
</tr>
<tr>
<td>13. Is separation of non-compatible animals considered?</td>
<td>13</td>
<td>14 97 1 463</td>
</tr>
<tr>
<td>14. Are laboratory personnel instructed in least stressful procedures?</td>
<td>5</td>
<td>26 448 2 99</td>
</tr>
</tbody>
</table>

15. Is pain-killer described?
16. If curare drugs are used, are they used with an anesthetic?
17. Is the lack of a pain-killer argued?
18. Is surgical procedure described in detail?
19. Are presurgical norms established?
20. Are personnel trained for aseptic surgery?
21. Does protocol stipulate post-surgical observation?
22. Does protocol mention post-operative drugs and fluids?
23. Does investigator outline procedures for optimal recovery?
24. Is method of euthanasia described?
25. Do methods of euthanasia agree with ILAR specifications?
26. Is use of adverse procedures argued?
27. Is length of time of adverse procedure stated?
28. Is the intensity of the adverse procedure stated?
29. Are termination conditions set when using adverse procedure?
30. Does the investigator provide an assurance that only dead animals will be disposed of?

<table>
<thead>
<tr>
<th>Question</th>
<th>% Yes/No</th>
<th>Actual number of total responses of all four agencies</th>
</tr>
</thead>
<tbody>
<tr>
<td>15. Is pain-killer described?</td>
<td>34</td>
<td>109 195 18 253</td>
</tr>
<tr>
<td>16. If curare drugs are used, are they used with an anesthetic?</td>
<td>7</td>
<td>15 95 114 351</td>
</tr>
<tr>
<td>17. Is the lack of a pain-killer argued?</td>
<td>13</td>
<td>11 9 62 493</td>
</tr>
<tr>
<td>18. Is surgical procedure described in detail?</td>
<td>30</td>
<td>94 219 2 260</td>
</tr>
<tr>
<td>19. Are presurgical norms established?</td>
<td>11</td>
<td>26 218 2 329</td>
</tr>
<tr>
<td>20. Are personnel trained for aseptic surgery?</td>
<td>8</td>
<td>26 296 4 249</td>
</tr>
<tr>
<td>22. Does protocol mention post-operative drugs and fluids?</td>
<td>4</td>
<td>10 224 3 338</td>
</tr>
<tr>
<td>23. Does investigator outline procedures for optimal recovery?</td>
<td>16</td>
<td>38 196 3 338</td>
</tr>
<tr>
<td>24. Is method of euthanasia described?</td>
<td>17</td>
<td>72 171 193 139</td>
</tr>
<tr>
<td>25. Do methods of euthanasia agree with ILAR specifications?</td>
<td>13</td>
<td>58 12 367 138</td>
</tr>
<tr>
<td>26. Is use of adverse procedures argued?</td>
<td>68</td>
<td>131 54 7 383</td>
</tr>
<tr>
<td>27. Is length of time of adverse procedure stated?</td>
<td>52</td>
<td>100 89 2 384</td>
</tr>
<tr>
<td>28. Is the intensity of the adverse procedure stated?</td>
<td>55</td>
<td>107 83 3 82</td>
</tr>
<tr>
<td>29. Are termination conditions set when using adverse procedure?</td>
<td>21</td>
<td>39 142 3 391</td>
</tr>
<tr>
<td>30. Does the investigator provide an assurance that only dead animals will be disposed of?</td>
<td>9</td>
<td>39 388 12 136</td>
</tr>
</tbody>
</table>
### TABLE III
Comparison Between 1972 and 1976 for Four Selected Questions for the Four Agencies

<table>
<thead>
<tr>
<th>Question</th>
<th>Agency</th>
<th>%Yes/Applicable Responses 1972</th>
<th>%Yes/Applicable Responses 1976</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1-Is the use of animal-model approach argued?</td>
<td>NIAAA</td>
<td>38</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>NIDA</td>
<td>48</td>
<td>49</td>
</tr>
<tr>
<td></td>
<td>NIMH</td>
<td>35</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td>NSF</td>
<td>78</td>
<td>82</td>
</tr>
<tr>
<td>A2-Is the possibility of &quot;alternatives&quot; explored?</td>
<td>NIAAA</td>
<td>20</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>NIDA</td>
<td>11</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>NIMH</td>
<td>23</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td>NSF</td>
<td>84</td>
<td>85</td>
</tr>
<tr>
<td>B2-Is the model chosen as representing the most accurate simulation?</td>
<td>NIAAA</td>
<td>25</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>NIDA</td>
<td>33</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>NIMH</td>
<td>43</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>NSF</td>
<td>78</td>
<td>79</td>
</tr>
<tr>
<td>B3-Is Choice of species (strain, breed) argued in terms of least cost to environment and least stress?</td>
<td>NIAAA</td>
<td>13</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>NIDA</td>
<td>2</td>
<td>6</td>
</tr>
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<td></td>
<td>NIMH</td>
<td>21</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td>NSF</td>
<td>57</td>
<td>66</td>
</tr>
</tbody>
</table>

### TABLE IV
Percentage of Positive Responses for Applications Funded in 1972

<table>
<thead>
<tr>
<th>Agency</th>
<th>%Applications Reviewed</th>
<th>Validity</th>
<th>Efficiency of Utilization</th>
<th>Methods</th>
<th>Stress/Facilities</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIAAA</td>
<td>32</td>
<td>49</td>
<td>19</td>
<td>60</td>
<td>13</td>
</tr>
<tr>
<td>NIDA</td>
<td>55</td>
<td>45</td>
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<td>47</td>
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</tr>
<tr>
<td>NIMH</td>
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<table>
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<tr>
<th>Agency</th>
<th>%Applications Reviewed</th>
<th>Validity</th>
<th>Efficiency of Utilization</th>
<th>Methods</th>
<th>Stress/Facilities</th>
</tr>
</thead>
<tbody>
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<td>NIAAA</td>
<td>24</td>
<td>60</td>
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<td>68</td>
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<td>NIDA</td>
<td>47</td>
<td>53</td>
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<td>NIMH</td>
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<td>397</td>
<td>62</td>
<td>43</td>
<td>70</td>
<td>18</td>
</tr>
</tbody>
</table>
DISCUSSION

The review and evaluation of awarded grant applications reveals that there had been little improvement in the explicit attention given to the use of the most appropriate research model and the subsequent care for that model over the four year period. However, sufficient numbers of grant applications addressed the areas of concern raised in the questionnaire, indicating that it was not unreasonable to expect such questions to have been answered.

The present study does, however, reflect on the peer review committees who are responsible for assessing the grant applications for approval and funding. Theoretically, the grant applications should indicate that they comply with the requirements set out in the guidelines for the Responsibility for Care and Use of Laboratory Animals (NIH, 1971) if they are to be successful. As is evident from Table II, many of the grant applications contained insufficient information for the peer review committees to have made a reliable assessment unless supplementary information had been obtained. For example, there were very few applicants who addressed questions concerning:

a) The number of animals required;
b) Evidence of a literature search for statistical methodology, animal housing and care;
c) Minimizing the stress suffered by an animal during the experiment itself; and
d) Provisions for physical and psychological comfort for the chronically housed animal.

The peer review committees represent by definition, the knowledge and attitudes of the scientific community. Therefore, it is not unreasonable to assume that, on balance, the individual is also neglecting some of the animal welfare questions raised in the present study.

Recently, the National Institutes of Health has revised its Animal Welfare Policy to require a more stringent commitment from institutions receiving NIH grants or contracts to comply with the appropriate provisions for the care and treatment of laboratory animals. The revised principles regarding the use of laboratory animals are now published in the Guide for the Care and Use of Laboratory Animals (ILAR, 1978). Some major changes in the revised Policy include:

a) The principles for the use of animals will apply to all live vertebrates, not just warm-blooded animals;
b) Grant applications will be expected to include sufficient information to assess the rationale for animal use, the precautions taken to avoid discomfort and injury, and whether or not the numbers proposed and the species to be used are appropriate to the problem being investigated;
c) Local committees will be encouraged to review proposals emanating from their institutions;
d) Statistical analysis, mathematical models or in vitro biological systems should be used when appropriate to complement animal experiments and to reduce the number of animals used;

An important element that remains unchanged is that no grant or award will be made unless the institution provides the required assurance that it will comply with the NIH Policy or its related Principles.

Annual utilization of research animals in the United States alone totals approximately 90-100 million. This number includes 20 million rats, 50 million mice, 3 million guinea pigs, 3½ million hamsters, and about 2 million rabbits. It is essential that the welfare (care and use) of these laboratory animals is taken into consideration by those investigators writing grant proposals, by peer review committees and by the funding agencies themselves.

RECOMMENDATIONS

Investigators, peer review committees and funding agencies are urged to respond to the results of this survey with full and explicit compliance to the already established animal care guidelines. A checklist to provide information in a clear and regular pattern to facilitate evaluation for approval and funding of a research project is recommended. Such a checklist would include:

a) Justification of the research and its potential benefit to mankind;
b) Assumptions inherent in using animal models and why alternative systems are not suitable;
c) Selection of a particular animal model and the numbers of animals required to achieve necessary statistical significance;
The checklist, in the form of a questionnaire, would ideally require only two columns, "Yes" and "Not Applicable". The checklist would be used by the investigator when preparing a grant application and signed and submitted, with supporting material where necessary, as part of the application. Such a procedure would also facilitate the peer review committees in assessing research proposals. The checklist could be used for all experiments involving laboratory vertebrates and need not necessarily be limited to grant-sponsored projects. A suggested checklist is provided in Table V.

It is the authors' opinion that the adoption of such procedures would not in any way jeopardize the freedom of the investigator to conduct research. In fact, such action is consistent with the publicly stated position of senior NIH personnel (Malone, 1977) and need not result in a significant increase in the amount of unproductive paperwork expected of applicants or of funding agencies.

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### TABLE V

**Suggested Checklist for Grant Application**

**A. Broad Aspects of the Research Description**

1. Has the project been justified in terms of animal or human benefit, potential benefit to the environment or development of knowledge base?

2. If animals are being used in the research, are reasons given why in vitro methods are not suitable?

3. Are the assumptions underlying the use of animals as models for man given and discussed?

4. Has a thorough literature search been conducted for:
   a) Prior work in the specified research area?
   b) Statistical design and analysis?

---

### B. Selection of the Animal Model and Minimizing Numbers Used

1. Are reasons given why the model selected is the optimum one for the particular research project?

2. Have factors such as evolutionary sophistication, genetic control, pathogenic control, knowledge base and status in the wild (if obtained from the wild) been considered in making choice?

3. Has the proposed source of the research animals been named?

4. Has the question of statistical significance and number of animals required to achieve the desired significance level been considered in the application?

5. Has the sequential use of animals been considered (e.g., using animals from another experiment excluding instances where the animal has already been subjected to severe trauma)?

### C. Methodological Descriptions

1. Is a step-by-step description of the methods to be used (including an outline of what will happen to the animal on the experimental table) provided?

2. Is a methodological design for interpreting and analyzing the data provided?

3. Are procedures for operative care described, including use (and type) of pain-killers and post-operative attention?

4. If any of the relevant personnel are not trained in the procedures necessary, will such training be provided before the start of the project?
5. Are the euthanasia methods described?

6. Do the euthanasia methods chosen conform to ILAR guidelines?

7. Are the reasons for the use of an adverse procedure (one in which the animal will be stressed or suffer pain while conscious or sentient) given?

8. Is the extent and duration of the adverse procedure explicitly described?

9. Where stress or pain will be suffered, has consideration been given to killing the animal when the stress does not justify continuation of the experiment?

D. Housing and Care

1. Has it been established that there are adequate facilities for the housing and care of the relevant laboratory animals which conform to ILAR/AAALAC guidelines, including:
   a) Surgical and post-operative care facilities?
   b) Noise control facilities?
   c) Separation of non-compatible animals?
   d) Veterinary support staff and trained ancillary personnel?
   e) Satisfactory exercise facilities?

2. Are animal housing conditions, such as the numbers of animals per cage and the question of housing in isolation, considered and/or argued?

REFERENCES


ILAR (Institute for Laboratory Animal Resources) [1978]: Guide for the Care and Use of Laboratory Animals. DHEW Publication No. (NIH) 78-23.


ACKNOWLEDGEMENTS

The authors wish to express their appreciation in the preparation of this manuscript to the following: Alfred G. Edward, Russell Lindsey, Frank Loew, Barbara Orlans, Richard H. Parker, and Harry C. Rowsell. While their advice and editorial comments have been of great help in writing this report, they do not necessarily endorse the views and conclusions expressed herein.
A. THE REVIEW PROCESS

Details of the questionnaire approach and reliability are given below.

a. The review team consisted of three research analysts (minimum qualifications of a basic biological sciences degree and some research experience required) and a coordinator.

b. The research analyst read through the applicant's entire proposal.

c. The analyst checked the personnel roster at the front of the application for the presence of veterinarian, laboratory technicians and animal care personnel.

d. If questions could not be answered yes or no, two alternatives were available. If the question did not apply to the proposal at all the analyst reported not applicable (NA). If the application did not provide enough information to respond positively or negatively to an applicable question, the analyst left the question blank (-----).

e. The investigator was given the benefit of the doubt where necessary and the questions were answered positively.

f. The analyst was told not to judge the validity or quality of the applicant's argument. Positive responses were recorded if the applicant had addressed the issue.

After each analyst completed ten questionnaires, the survey coordinator checked their understanding of the instructions by completing the form in blind study. Discrepancies were discussed in detail to eliminate sources of misinterpretation and error.

To check consistency, the survey coordinator examined two questionnaires for each of the research analysts after all three had completed at least 100 documents. The procedures were the same as above.

Two conferences were held to discuss possible differences in the manner each analyst answered each question.
There was no problem in distinguishing between positive, negative and non-applicable responses. The main difficulty occurred where the analyst had to make a decision between a negative and a blank (-) response. However, these two categories are interpreted in the same way in the final analysis (i.e., both are negative).

B. **THE PROJECT EVALUATION QUESTIONNAIRE FORM**

A. **Animal Modeling Approach**

1. Has the investigator clearly stated why the animal modeling approach is the best research method to answer his research question?

2. Has the possibility of tissue culture, organ culture, computer or other simulation procedures been explored?

3. Does the investigator indicate that his results are interpretable, using his chosen model, in terms of human utilization?

B. **Efficiency of Animal Use**

1. If he is repeating an already completed experiment, does the investigator justify the repetition?

2. Has the investigator stated an attempt to choose the most optimal model in terms of representing an accurate simulation of the larger object to be studied?

3. Is adequate justification presented for the choice of species and strain or breed in terms of such factors as least evolutionarily sophisticated, least endangered, least costly, most plentiful, etc.

4. Has the investigator addressed the choice of the least number of subject animals necessary for statistical significance?

5. Has the investigator named the source of his experimental animals?

6. Has the investigator examined the practicality of sequential utilization of animals which have been the subjects of an already completed research experiment and would otherwise be sacrificed?

7. Has the investigator attempted to reduce possible unwanted experimental variables which might negate his results?
   a) Attention to genetic control
   b) Attention to subject standardization through pre-experimental screening for uniformity and good health

8. Has the investigator examined the practicality of sequential utilization of his experimental subjects once he has completed his research?

C. **Quality of Methodology**

1. Is there evidence of literature searches (from the references) of the following:
   a) Prior work done in the specific research area
   b) Statistical analysis methodology
   c) Use of animal models in that particular research area

2. Does the investigator distinguish why his research is necessary in view of prior research in the field?

3. Are the objectives of the research specifically stated?

4. Has a methodological design for interpreting and analyzing the data been presented?

5. Is a description provided for the step-wise design of the experimental methodology?

6. Does the methodological description include what actually happens to the animal on the experimental table?

D. **Minimizing Stress/Adequacy of Facility**

1. Guide for Care and Use of Laboratory Animals (ILAR)

2. Are ILAR guidelines for floor areas and cage height followed?
3. Does the investigator indicate a methodological approach to, and the presence of physical facilities necessary for:
   a) Sterilization of equipment and supplies
   b) Experimental and surgical procedures
   c) Storage of food, bedding and supplies for the experimental animals
   d) Sanitation of facilities
   e) Disposal of waste, including special provisions for infectious, toxic or radioactive material
   f) Animal housing which provides screening of outside contaminants.

4. Are dietary requirements addressed?

5. Is the choice of the number of animals per cage defined?

6. Are the needs of exercise of the chronically housed animal addressed?

7. If the animals are housed in isolation, is this justified?

8. Are veterinary services for monitoring the good health of the subjects provided throughout the experiment?

9. Has noise control been addressed?

10. If restraint devices are used, is this justified?

11. If collar devices or earpunching and tagging are used as means of animal identification, are reasons given why alternative, less stressful means of identification weren't used.

12. Has the training of animal care personnel been addressed?

13. If animals from more than one species are subjects of the experiment, is the subject of room separation of inter-species animals which are natural enemies or carriers of infectious diseases addressed?

14. Is it stated that laboratory personnel are instructed on the least stressful way of performing the experimental protocol on the animal?

15. Is the type of anesthetic, analgesic or tranquilizer cited?

16. If curare drugs are used as surgical restraints, are they used in conjunction with an anesthetic?

17. If no anesthetic, analgesia or tranquilizing drugs are used, is a rationale presented for why not?

18. Is a step-by-step protocol for surgical procedures presented?

19. Are presurgical norms established by diagnostic testing prior to non-terminal surgery?

20. Are the laboratory personnel trained to perform aseptic surgery?

21. Does the protocol stipulate observation of the postsurgical animal until it is recovered from the anesthesia?

22. Does the protocol address administration of post-operative drugs and fluids?

23. Does the investigator address the post-operative procedures to assure the optimal recovery of the animal?

24. If the animal is sacrificed, is the method of euthanasia specified?

25. Do the methods of euthanasia correspond to ILAR's recommendations for that specific animal?

26. Is the use of the adverse procedures such as shock, restraint, confinement, isolation, deprivation, starvation or overcrowding justified?

27. Is the length of time of an adverse procedure stated?

28. Is the intensity of the adverse procedure stated?

29. If a physical or psychological effect of an adverse procedure is anticipated as the result of an experiment, is an attempt made to define the conditions under which the effect expected will be considered sufficient to terminate the stress on the animal?

30. Is there an assurance presented that no animal will be disposed of without first ascertaining that it is dead?
C. ANALYSIS OF QUESTIONNAIRE RELIABILITY*

What is the reliability of the questionnaire used in this study? The design of this study required that three observers each evaluate a different set of biomedical research grants through use of the questionnaire. To test reliability, each of the three observers evaluated the same set of fifteen grants selected at random. The results of one observer were then compared with each of the results from the other two observers. Results of the analysis were:

<table>
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<tr>
<th>Evaluator</th>
<th>Validity Mean</th>
<th>Validity Variance</th>
<th>Resource Utilization Mean</th>
<th>Resource Utilization Variance</th>
<th>Methodology Mean</th>
<th>Methodology Variance</th>
<th>Minimization of Stress Mean</th>
<th>Minimization of Stress Variance</th>
<th>Facilities Mean</th>
<th>Facilities Variance</th>
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<td>.024</td>
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<td>.044</td>
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<td>.020</td>
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<td>.029</td>
<td>.322</td>
<td>.046</td>
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</table>

**The original analysis divided stress and facilities into separate categories. These were later combined in the main report.

Figures in the table show that the means and variances are consistent for each of the five evaluative criteria.

This is a reassuring finding, but it is not an altogether sufficient test. Despite the fact that the measures of central tendency and dispersion are very close, there remains the possibility of inconsistent evaluation of individual grants. To pursue this concern, a two-way analysis of variance was conducted for each of the five criteria. This provides, among other things, a measure of the variation in criterion scores attributable to difference in the observers, holding constant the grant being evaluated. Results are summarized below.

**ANALYSIS OF VARIANCE TABLE**

<table>
<thead>
<tr>
<th>VALIDITY</th>
<th>RESULTS</th>
<th>METHODS</th>
<th>STRESS</th>
<th>FACILITIES</th>
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<td>Sq.</td>
<td>Sq.</td>
<td>Sq.</td>
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<tr>
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<td>F</td>
<td>F</td>
<td>F</td>
<td>F</td>
</tr>
<tr>
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<td>.010 3.73</td>
<td>.001 1.00</td>
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<tr>
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<td>.313 11.96</td>
<td>.056 9.94</td>
<td>.037 13.84</td>
<td>.079 99.44</td>
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</tbody>
</table>

This table shows first, that variation in criterion scores (as measured by mean squares) attributable to difference in observers is dwarfed by that attributable to difference in grants; secondly, with (2, 28) degrees of freedom, the F ratios for observer effects are all statistically insignificant at the .01 level, and only one—the methodology criterion—is significant at the .05 level. Consequently, the questionnaire is judged to be reliable in the technical sense of that term.

D. EXPLANATION OF THE INTERPRETATION APPLIED TO
SOME OF THE QUESTIONS AND THE POSSIBLE
RESPONSES.

Question(s)

A2  If the study was strictly behavioral (no
     manipulation of the experimental animal) it
     was considered NA.

B6  If the study called for a germ-free, fetal or
     neonatal animal, it was considered NA.

B7a & b  These questions were concerned with the
     differences between random source and
     laboratory bred animals. If the animal was
     used merely as a source for tissue or organ
     material, it was recorded as an NA.

B8  If the animal was sacrificed immediately upon
     completion of surgery, an NA response was
     recorded.

Section C

Where appropriate in Section C, if the animal
was killed at the onset as a source of tissue
or organs, an NA response was recorded.

C6  If the investigator was developing a new
     technique then an NA response was recorded

Section D

As in Section C, if the animal was killed
immediately on arrival, then an NA response
was recorded.

D2  AAALAC, AALAS or HEW specifications (or
     unreferenced figures which conform to these
     guidelines) were acceptable.

D7  A blank was recorded if the investigator did
     not even mention the number of animals per
     cage.

D8  A positive response may have been derived
     from an inspection of the personnel roster
     at the front of the form or from a statement
     describing animal housing under veterinary
     care.

D10 A blank response was recorded if there was
     any suspicion that restraint was part of the
     experimental procedure (e.g., mention of a
     restraint device in the list of supplies)
     although it might not have been mentioned in
     the actual proposal.

D11 A blank response was recorded if the need
     for identification is evident or suspected
     but was not mentioned in the application.
     (Both D10 and D11 require some interpretation
     on the part of the analyst).

D12 See D8

D13 An NA response was recorded if only one
     species was under investigation.

D15 An NA response was recorded if no anesthesia
     was required. A blank (or no) response
     was recorded if anesthesia appears to be part
     of the protocol but the description is too
     sketchy to make a proper evaluation.

D16 A blank response was recorded when the
     application mentioned the use of an anesthetic
     but it was not possible to determine whether
     or not a curariform drug was used. As a
     result, the final figure would have a negative
     bias since some of the studies would be using
     actual painkillers.

D17 A blank response was recorded if the methods
     description was too vague or ambiguous to
     determine if anesthetics were used or not.

D18 An NA response was recorded if the
     investigation was an intervention-type
     observational study, or when it was stated
     that the animal would be kept alive for
     further experiments. A blank response was
     recorded if the final disposition of the animal
     was not addressed at all.

D24 See D24

D25 An NA response was recorded if no adverse
     conditions are investigated. Blank responses
     were recorded when the equipment requisition
     section indicated that adverse procedures
     might be involved. (N.B. This question was
     addressed only to studies that investigated
     the physical or psychological consequences
     of adverse external conditions on the animal
     model. It did not include such things as
     restraint, which was required by the
     procedures used in some other type of
     investigation - e.g. investigation of drug
     habituation).

D26-D29
E. ANALYSIS OF THE RESULTS TO GIVE AN INDICATION OF THE MEASURE OF DISPERSION

Table IVa has been drawn up to provide a measure of the dispersion of the results. The ratio of the total number of positive responses to all applicable responses was calculated for each section of each grant review (the analysis was done for five sections, stress minimization and facilities being placed in two separate categories – question D3a-f formed the facilities category). Thus, there are five different figures for each grant. The means of the figures for each category and each agency were then calculated together with the variance.

| TABLE IVa |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Ratios of Favorable Responses to Applicable Responses for Grants Funded in 1972 |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| NIAAA | 32 | .490 | .188 | .595 | .158 | .083 |
| | | (.063) | (.012) | (.022) | (.018) | (.034) |
| NIDA | 55 | .454 | .123 | .473 | .178 | .082 |
| | | (.126) | (.020) | (.032) | (.009) | (.026) |
| NIMH | 153 | .383 | .207 | .615 | .209 | .133 |
| | | (.117) | (.037) | (.025) | (.041) |
| NSF | 144 | .594 | .422 | .692 | .161 | .228 |
| | | (.098) | (.068) | (.035) | (.034) | (.069) |
| All Agencies | 384 | .481 | .274 | .622 | .182 | .157 |
| | | (.115) | (.058) | (.038) | (.026) | (.052) |

Ratios of Favorable Responses to Applicable Responses for Grants Funded in 1976
Variances are given in (parentheses).

<table>
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<tr>
<td>All Agencies</td>
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<td>.369</td>
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<td>(.107)</td>
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