Animal Experimentation in Cancer Research: A Citation Analysis

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Cancer research involves the use of millions of nonhuman animals and billions of dollars in public funds each year, but cures for the disease remain elusive. This article suggests ways to reduce the use of animals and save money by identifying articles that garnered few citations over the 9 years after they were published. I obtained the citations received by 786 articles in 9 general cancer journals published in 1990 and the number of animals used (where possible) in the 220 animal-based research articles. By calculating the ratio of animal number to citation number, I identified the most effective (those with many citations and few animals used) and the least effective (those with many animals and few citations) articles. Using these ratios, I compared the effectiveness of their experiments/articles for the 9 journals, author affiliations and nationalities, and funding sources. This article recommends ways in which experiments with little chance of being influential can be avoided, thus freeing resources for more worthwhile assaults on cancer.

The search for a cure for cancer is a vast international enterprise using many millions of nonhuman animals and billions of dollars each year. Scientists determine retrospectively by their subsequent citations (or lack of citations) which of the enormous number of experiments/articles were worth publishing. This citation information can be used to recommend ways of decreasing the waste of animal lives. The money for cancer research saved then can be focused either on clinical and epidemiological studies or on environmental causes of the disease.

The aim of this study was to determine if cancer research could be more accountable in its use of animals in experimentation and therefore more responsible in use of public monies, which largely fund the research. The United States spends

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more than $2 billion a year on cancer research (Medical Research Modernization Committee, 1999). The quality of research articles can be judged by peer reviewers reading and evaluating the articles or, in a more efficient and less biased method, by noting the number of citations the articles subsequently garner (Rochon, Gurwitz, Cheung, Hayes, & Chalmers, 1994).

A previous study showed that many psychological and neurological experiments carried out on large numbers of animals yielded few citations, suggesting that few researchers found the results worthy of pursuing—or even mentioning—in their own research findings (Dagg, 1999). In a few cases, this might mean that the field of research was limited and has remained so. In most cases, however, this further suggests that the animals used in the research suffered stress, pain, and (usually) death for no good purpose.

This article focuses on cancer research, of more central concern to human beings. Because of soaring medical costs, cost-effectiveness analyses increasingly are recommended for cancer research projects to ensure that funding is not wasted (Waters, 1998). People want to know that the money they donate for cancer research is well spent. Although most people accept the need for animal research to combat disease, they are increasingly uncomfortable with research involving pain or death to animals, particularly if there is reason to believe that the research will contribute little to our knowledge (Shapiro, 1998).

The pressure to use fewer animals in experimental research has been longstanding and widespread. Although animal experiments are cheaper and quicker than human clinical research, they are inadequate for a number of reasons, one of which is that substances that do not cause cancer in animals might do so in human beings (Proctor, 1995). Although many alternative techniques have been devised to reduce the use of animals, scientists have refused or been slow to adopt them (Langley, 1989; Marx et al., 1997; Orlans, 1993). The number of animals used in science, of which cancer research is a prominent component, has not decreased significantly in recent years and remains enormous, especially with the recent increase in transgenic experimentation. In Canada, about 1.4 million animals are used in all experimental research each year (Canadian Council on Animal Care, 1999); in the United Kingdom, about 2.8 million (Festing, 1998); the United States uses well over 50 million rats and mice (statistics on these species are not kept routinely) as well as more than 1.2 million other species (Menon, 2000; U.S. Department of Agriculture, 1997).

### METHOD

I chose for study the 1990 issues of the nine general cancer research journals held in the library of the University of Waterloo, which does not have a medical faculty (Table 1). The year’s early issues were examined for each journal. I tab-
ulated no more than 100 experimental research articles for any one journal, sometimes less if fewer that year were published or if the issues published subdisciplines separately and sequentially, so that the results would be biased if only part of an issue were included.

Each article, according to its use of animals, was assigned to one of three categories:

A: Research focused on animals, with species, strains, and conditions of housing usually described in Methods and Materials sections. Tables and figures in the articles usually were devoted to animals, giving such data as survival from treatments or number of tumors present related to the number of individuals injected. Mice and rats were by far the most common species, although fish, hamsters, rabbits, dogs, ferrets, shrews, and monkeys also were used.

T: Research focused on tissue, from either cancer patients or a few animals; if more than six animals were used, the article was classified as A. Tissue from human patients or animals usually was treated with chemicals or with sera from various animal species: fetal calf serum, goat antirabbit immunoglobulin G, mice monoclonal antibodies, murine fibrosarcoma cells, and so on. Sometimes mice were inoculated to test for a substance’s tumorigenicity; again, if more than six animals were involved, the article was included in Category A.

### TABLE 1

Percentages of Types of Experiments/Articles in Nine Cancer Journals—Listed From Least to Most Articles Involving A-Type Experimentation

<table>
<thead>
<tr>
<th>Journals</th>
<th>No. of Articles Surveyed</th>
<th>% Focused on</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Animals</td>
<td>Tissues</td>
<td>Human Beings</td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>99</td>
<td>4</td>
<td>33</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>British Journal of Cancer</td>
<td>88</td>
<td>18</td>
<td>48</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>International Journal of Cancer</td>
<td>88</td>
<td>20</td>
<td>5</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>British Journal of Radiation Oncology Biology Physics</td>
<td>92</td>
<td>22</td>
<td>63</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>International Journal of Cancer</td>
<td>92</td>
<td>22</td>
<td>63</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Journal of the National Cancer Institute</td>
<td>99</td>
<td>32</td>
<td>39</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>Cancer Research</td>
<td>100</td>
<td>34</td>
<td>61</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Japanese Journal of Cancer Research</td>
<td>85</td>
<td>39</td>
<td>54</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Nutrition and Cancer</td>
<td>54</td>
<td>44</td>
<td>11</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>Carcinogenesis</td>
<td>81</td>
<td>48</td>
<td>51</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>786</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Animal Use in Research Projects

Virtually all animals in cancer experiments were subjected to invasive procedures, namely at Levels 4 and 5—the most extreme measures—of the Scale of Invasiveness (Shapiro, 1998). They frequently were inoculated, which itself causes stress (Sapolsky, 1990), or given a xenograft or gavage treatment to cause the growth of tumors; often they then were given experimental chemical, radiation, or heat treatments to combat the tumors. Sometimes, hundreds of animals were injected with varying doses of a chemical to see what dose killed them and how quickly they died. Usually, control animals also were involved in invasive procedures; thus, they too were included in the total number of animals used. However, I did not include females who gave birth to young used in experimentation or who produced fetuses to be used in experimentation. The assumption was that the adult animals were not treated any worse than other animals not involved in experimentation and that the fetuses, because they were immediately killed, did not suffer unduly.

For each article, the number of animals invasively involved was calculated, with the average used if a range was given (e.g., 9–15 animals were used in each experiment). This number was often difficult, and sometimes impossible, to establish from the text (although its lack surely should decrease the value of the article). For example, often rat or mouse tissue was used without indicating how many individuals supplied it. If there was doubt about the total, the minimum value was used. In some cases, the total could not be calculated because it was too uncertain; therefore, these articles are included only for Tables 1 and 2 and are in no figures. In many experiments, further unknown numbers of animals were used because the text stated that preliminary studies had been done or that further experiments had been completed but the results were not included. Thus, the numbers of animals included in Tables 1 and 2 are always a minimum and usually an underestimate of the actual use of animals.

Number of Citations for Animal Experiments/Articles

For each article analyzed, the number of citations it received from 1990 to Fall 1999 was obtained from the Institute for Scientific Information through a University of Waterloo Watmars Search. It is assumed that the more citations an article received, the more useful its results were to the work of subsequent researchers. Articles, of course, may be self-cited by the author or cited because of
faulty results, in which case the number of citations gives an overly optimistic impression of the article’s influence. By contrast and with rare exceptions (Dagg, 1999), an article that has few or no citations has been of little or no use to other scientists.

### Analysis of Data

Large numbers of animals used in an experiment would seem, from an animal perspective, to be less disturbing the greater the number of citations the experiment/article subsequently garnered. Or, put another way, an article that received no citations would seem less upsetting the fewer the animals used. In assessing how problematic an article is, one must consider both the number of animals used and the number of citations received. Thus, to analyze the collected data most effectively, I divided the number of animals used for each experiment/article by the number of citations that the article received in the next 9 years. The lower the value of this equation, the greater the justification for the pain inflicted on the animals; from a research perspective, an article that re-

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**TABLE 2**

Average Number of Citations for All Articles, Animal Articles, and Nonanimal Articles for Nine Journals—Listed in Order of Effectiveness

<table>
<thead>
<tr>
<th>Journals</th>
<th>Average No. of Citations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Articles 220 Animal Articles</td>
</tr>
<tr>
<td>Journal of the National Cancer Institute</td>
<td>52 47 54</td>
</tr>
<tr>
<td>Cancer Research</td>
<td>41 25 49</td>
</tr>
<tr>
<td>Cancer</td>
<td>28 25 28</td>
</tr>
<tr>
<td>International Journal of Cancer</td>
<td>28 15 32</td>
</tr>
<tr>
<td>Carcinogenesis</td>
<td>26 23 29</td>
</tr>
<tr>
<td>British Journal of Cancer</td>
<td>25 11 28</td>
</tr>
<tr>
<td>International Journal of Radiation Oncology</td>
<td>19 15 21</td>
</tr>
<tr>
<td>Japanese Journal of Cancer Research</td>
<td>16 15 17</td>
</tr>
<tr>
<td>Nutrition and Cancer</td>
<td>14 10 17</td>
</tr>
<tr>
<td>Totals</td>
<td>249 186 275</td>
</tr>
<tr>
<td>Averages</td>
<td>28 21* 31*</td>
</tr>
</tbody>
</table>

*These values were significantly different (paired t test).
received no citations has virtually no scientific value compared with one that received many citations, even though it used many animals.

Other Information Collected From the Articles

In addition to the number of animals used and the number of citations received, I noted for each Category A article the authors’ nationality and the research sector’s affiliation (governments including centers, institutions, and hospitals not connected to a university; universities or colleges; foundations; or commercial businesses). I also noted the funding, if any, each one acknowledged as underwriting the research (governments and nongovernment groups such as charities, foundations, or commercial businesses) and the number of authors listed for each article. Using the data collected for all the 786 articles, I considered two questions:

1. Which journals on average published the most and the fewest experiments/articles that focused on animals and therefore reflected the most and least amount of total trauma to animals (Table 1)?

2. Which journals on average for all their articles are the most cited and which the least, and, therefore, which are the most and least valuable to cancer researchers? Do animal-focused and non–animal-focused experiments/articles receive equal numbers of citations (Table 2)?

I assume there is an ethical problem for experiments/articles that used many animals but received few or no citations. Questions 3–8 address the 186 Category A articles that focused on animal research and for which the number of animals could be calculated from the 220 Category A articles:

3. Which journals have the most effective animal-based research judging from the animal number over citation number (AN/CN) values for their Category A articles (Table 3)?

4. Do these values vary with the authors’ nationalities? A multiauthored article was included under as many nationalities as the affiliations indicated (Figure 1).

5. Do these values vary for authors affiliated with governments, foundations, universities, or commercial concerns? If authors had more than one of these affiliations, they were considered under each category (Figure 2).

6. Do these values vary depending on funding agencies? Again, all funding agencies were considered under each category if there were more than one (Figure 3).

7. Do these values vary depending on the number of people who conducted the experiments?
TABLE 3
Comparison of A-Type Articles for Nine Cancer Journals in Order of AN/CN Values

<table>
<thead>
<tr>
<th>Journals</th>
<th>No. of A-Type Articles for Which Animal Numbers Could Be Recorded</th>
<th>Average AN/CN Values*</th>
<th>% of Articles Where CN &gt; AN</th>
<th>% of Articles Receiving 0, 1, 2, or 3 Citations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>4</td>
<td>2</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>Journal of the National Cancer Institute</td>
<td>29</td>
<td>3</td>
<td>38</td>
<td>6</td>
</tr>
<tr>
<td>Carcinogenesis</td>
<td>32</td>
<td>7</td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td>Japanese Journal of Cancer Research</td>
<td>13</td>
<td>9</td>
<td>11</td>
<td>52</td>
</tr>
<tr>
<td>International Journal of Cancer</td>
<td>27</td>
<td>11</td>
<td>18</td>
<td>25</td>
</tr>
<tr>
<td>International Journal of Radiation Oncology</td>
<td>17</td>
<td>11</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>Cancer Research</td>
<td>24</td>
<td>14</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>British Journal of Cancer</td>
<td>12</td>
<td>15</td>
<td>8</td>
<td>31</td>
</tr>
<tr>
<td>Nutrition and Cancer</td>
<td>28</td>
<td>16</td>
<td>21</td>
<td>29</td>
</tr>
<tr>
<td>Total</td>
<td>186</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note. AN = animal number; CN = citation number.

*The AN/CN values were significantly different between journals, $F = 3.2, p = .002$.

FIGURE 1  Values of the animal number over citation number for the three or more articles of authors of 10 nationalities, the most effective at the left. Sample sizes were 3 (Norway), 5 (Canada), 97 (United States), 7 (Netherlands), 4 (China), 7 (Germany), 15 (United Kingdom), 49 (Japan), 6 (Italy), and 4 (France).
FIGURE 2  Values of the animal number over citation number for the four affiliations of the articles' authors, the most effective at the left. Sample sizes were 3 (foundations), 97 (governments), 17 (commercial businesses), and 129 (universities).

FIGURE 3  Values of the animal number over citation number for the five acknowledged funding groups, the most effective at the left. Sample sizes were 19 (foundations), 112 (governments), 50 (nongovernmental groups), 9 (commercial businesses), and 10 (universities).
8. Is research that involves only rats and mice equally as effective, judging by the ratio values, as that involving other less commonly used species?

RESULTS

Judging from the proportions of the three types of articles that comprise each issue (Table 1), different journals have different priorities in what they publish. In Cancer, 4% of articles were based on animal research, whereas Carcinogenesis had 12 times as many. From an animal perspective, the former journal compared with the latter therefore reflects experiments on relatively few animals. In only two journals were there more animal than tissue studies, whereas the number of human studies was highly variable.

Table 2 gives the effectiveness of each journal, judging from the average number of citations received from all the 220 Category A articles. The Journal of the National Cancer Institute is thus by far the best journal, and Nutrition and Cancer is the worst. When the average numbers of citations for all the animal-based articles and all of the rest were calculated for the journals (Table 2), the Category A articles garnered many fewer citations on average (21) than did the other articles (31), with values significantly different (paired t test).

When the averages of AN/CN values for the 186 Category A articles were calculated, they varied widely among journals (Table 3). Analysis of variance (omitting the four very high values noted subsequently) showed that the AN/CN values were significantly different between journals, $F(8, 176) = 3.2, p = .002$. There was a large variation in these values in most journals, especially the British Journal of Cancer and the Japanese Journal of Cancer Research. Cancer and Journal of the National Cancer Institute were the most effective journals with the lowest values and the greatest percentage of articles in which the citation numbers exceeded the animal numbers. Nutrition and Cancer was the least effective journal, with an average of 16 animals being experimented on for every citation received.

When the percentage of articles that received only zero, one, two, or three citations during the 9-year period after publication was calculated, the Japanese Journal of Cancer was the least effective, with more than half of its articles receiving fewer than four citations each. Four articles of the 186 received more than 100 citations: three in the Journal of the National Cancer Institute (101, 185, and 275 citations) and one in the Japanese Journal of Cancer (173 citations).

Authors of the 186 Category A sample of articles had affiliations with 22 countries. If one article had authors with affiliations to several countries, the AN/CN values were included for analysis under each country. Twelve of these countries were represented by only one or two articles with AN/CN values, whereas the other 10 had from 3 to a maximum of 97 articles (for authors whose stated affiliation was the United States). In order of efficacy (low to high AN/CN values), these
countries were Norway, Canada, the United States, Netherlands, China, Germany, the United Kingdom, Japan, Italy, and France (Figure 1).

The authors’ affiliations again were listed under several categories if necessary. Figure 2 shows that authors based in foundations produced the most efficient experiments/articles, followed by governments; commercial interest and university values were the same and the least efficient. For funding, foundations and governments were the most successful supporters (Figure 3); much less successful were nongovernment agencies, commercial interests, and universities.

There was no obvious correlation between the number of researchers who worked on an experiment/article and the AN/CN values their articles received. I compared the AN/CN values for the large number of experiments on rats and mice with those few on other animals but found no striking difference between them.

**DISCUSSION**

There is a wide gap in data between the average citation records of articles published in the best journals and those in lesser journals, a gap that should concern all scientists. For animal-based experiments/articles that are included in each of these journals, some were far more influential than others, judging by the citations they received (Wade, 1997). Because on average animal-based experiments/articles garnered significantly fewer citations than did other types of cancer experiments, it would seem sensible to focus more attention on the latter. This goal is logical because epidemiological and clinical studies have been especially useful in addressing problems of cancer in people (Preece & Chamberlain, 1993).

Some countries were far more successful than others in producing animal-based experiments that other researchers judged useful. It would seem worthwhile for the least successful countries such as France, Italy, Japan, and the United Kingdom to reconsider their animal-based cancer research programs that seem to have been relatively unproductive yet costly in finances and in animal lives.

The large research efforts of universities (129 articles) were less productive than were those of foundations and governments, presumably because they were less careful in choosing what experiments to perform but also because they are in a better position than other bodies to take risks. The financial stake in cancer research is so great that thousands of graduate students and postdoctoral fellows are drawn to the field in university laboratories, each of which has research projects that often involve animals. The frantic search to obtain one of the limited permanent positions might explain the large number of cancer experiments—carried out at great cost—that engender few or no citations in subsequent years. It might be that animal care committees of universities—although in place—are unable or unwilling to forbid experiments that seem likely to be unproductive. If one researcher votes against a colleague’s proposal, he or she might fear retaliation in the future.
RECOMMENDATIONS

I offer five recommendations to reduce the unnecessary use of animals in experimentation and to reduce financial waste:

1. Researchers should ensure that animals are used in an experiment only if no alternative feasible methods of research are available.
2. Researchers should undertake small pilot studies first for animal experimentation to ensure that a larger experiment is worth conducting.
3. Researchers should receive promotions and honors only for carrying out quality research that is cited frequently.
4. Applications for funding should require researchers to list citation counts for their earlier research publications.
5. Each published article should state clearly what measures were taken to reduce pain to the animal subjects and should indicate how many animals were used in experimentation. These data aid in assessing the validity of the experiments.

GENERAL DISCUSSION

In the past, scientists have been blamed for performing “do and see” research, doing experiments on animals without any clear rationale or theory (Weinberg, 1996). This type of research still seems to be en vogue, judging by the many animal-based articles on cancer that received few or no citations. Research scientists often viewed their animals with no more empathy than if they were test tubes—both usually can be purchased in quantity from a supply house—despite stating publicly that the animals were both an essential and integral part of endeavors to solve problems of cancer. Sometimes the animals were not even mentioned in the Material and Methods section, and usually their numbers were not explicitly given, indicating condescension (Shapiro, 1998).

As an example of the attitude of scientists, Weinberg (1996) wrote that in the early days of cancer research on animals, the work “seemed to be going nowhere, a research field littered with the bodies of thousands of scientists who had spent their lives fruitlessly trying to figure out what cancer was all about” (pp. 20–21). Yet, in reality, it was the millions of mice and rats who suffered and died—a point that Weinberg ignored—whereas the researchers had relatively successful, well-paid careers.

Although generally considered to be “a forward-looking, progressive activity” (Langley, 1989), science has been unwilling to recognize the need to save money and animal lives by reducing where possible the large number of animal-based experiments it has indicated are worthless. Many millions of animals have died because scientists have delayed implementing new and improved techniques in their
laboratories (Langley, 1989). Researchers too often suffer from complacency, failure of imagination, orthodoxy, and inertia, whereas governments have been slow to update regulations and push for the use of alternative methods of research where possible (Langley, 1989).

If the way cancer research is carried out is to change, such change must be instigated by the public, who largely funds the research. Without such a stimulus, it seems certain that most researchers will continue to use animals, often in large numbers, even if their experiments are of little or no interest to other researchers. After all, such research in the past has enhanced their professional and pecuniary interest (Preece & Chamberlain, 1993). If fewer animal-based experiments with little hope of much success are performed, the money saved can be used to combat cancer in other ways, such as addressing environmental causes.

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REFERENCES


