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For Literature Searches, Is Medline Enough?

Dr. Eduardo Morales' research on the maturation of the immune system included the subcutaneous implantation of an osmotic pump between the scapulae. Thin tubing exited the pump and entered the external jugular vein. Morales performed this protocol in hamsters, aseptically, under general anesthesia and with the use of postprocedural analgesia.

As part of its IACUC application process, Great Eastern University required investigators to perform a literature search for possible alternatives to pain, distress, or animal usage. Morales had always done so without question, and as is common with many investigators, he searched the Medline database from 1966 to the present. The key words he used, in various combinations, included 'hamster', 'alternative', 'in vitro', 'immunity', 'immune system', and the name of the particular compound that he was using. He also listed any pertinent scientific meetings he had attended. Invariably, he told the IACUC that there were no viable alternatives to the use of animals or to the procedures he had used. Also invariably, the IACUC did not question this.

Paula Stone, the University's librarian, received an appointment to the IACUC to "help investigators do a more rapid literature search". Soon, there was a hint of conflict in the air. Stone, who had been trained by the staff of the National Agricultural Library, made it clear that she truly wanted to help the investigators and would gladly work with them to develop general search strategies, but she did not have the resources to do all the searches for them. In the few instances when she would actually do a search for an investigator, it would be on a fee-for-service basis. This was not what many people wanted to hear. Stone turned to the Morales protocol. She said

that Medline is simply not a good database to use for seeking alternatives, that one should not use it as the only database, and that the search terms Morales had used, though seemingly reasonable, were unlikely to uncover alternatives. Rather than have a prolonged discussion during the meeting, the Chairwoman thanked Stone for her insights and said that she would speak privately with her about her concerns.

The following week Stone presented a search scenario that the Chair, who was a scientist, knew was far more complicated and lengthy than any researcher at Great Eastern would accept even if additional databases became available. The Chair emphasized that the key words used by Morales included all of the main terms for an alternatives search that was performed at most other universities, and, in any case, searches (in her experience) never turned up any viable alternatives. Furthermore, she said that researchers were very aware of new developments in their field and would know about any nonanimal alternatives. She suggested that Stone perform her own search on any or all of the 12 protocols reviewed at the last meeting, and if she could find any reasonable alternatives to the procedures that the IACUC had approved, she would personally ask the Vice President for Research to provide funding for a librarian to be assigned specifically to IACUC functions. Stone could not afford the time that such a challenge would entail, and she also felt that the Chair was denigrating her purpose for being on the IACUC.

Did Morales perform an adequate literature search that met the word and spirit of the USDA regulations, or is Stone correct in implying that a better search was needed? If improved searches are necessary, how can the Great Eastern IACUC and its

investigators accomplish this within the constraints of a busy research schedule?

Perception of an Adequate Literature Search

A. Lee Shuman, AS, CAHT

The Animal Welfare Information Center (AWIC) provides information on its website¹ about techniques that one can use for literature searches that will comply with Animal Welfare Act Regulations. According to the guidelines, the search should involve at least two databases. Although Morales may have been familiar with ongoing research in his field, it is the perception of an adequate search that is the issue at hand rather than whether or not alternatives could be found. There seems to be no question that his methods and objectives were sound, but that the literature search should have been more comprehensive. The AWIC "Alternatives and the Animal Welfare Act" brochure² suggests that 'alternative' alone may not be the most appropriate keyword to use in a literature search. Perhaps he could have added 'animal model' to his key word list to expand the search.

There are many ways to comply with the University's requirement as to literature searches. In my view, the minimum search would have used the provided search terms but included at least two other databases. The library at my institution provides a mechanism to search several databases simultaneously and remove duplicates. I tried the search strategy used in the example with the exception of the compound name (not provided). Medline and Agricola did not have any matches, but Biosis had

six. These may very likely have been irrelevant to the proposed research, but using more than one database provides options that may not be available in only one.

The task of searching more than one database is not overwhelming in terms of time, nor does it require a trained librarian. Most investigators are familiar with the work of their competitors and are aware of current published work that is relevant to their proposed research. The value of an extended search is the possibility that one may find relevant work in another species. In the lab where I work, a Research Specialist does the literature search, often with suggested key words. Someone familiar with the work proposed is better suited to perform the search and able to evaluate the relevance of published literature on the topic than a nonscientist hired to perform the search.

References

1. Animal Welfare Information Center. Alternatives & Searches. <http://www.nal.usda.gov/awic/alternatives/alternat.htm>.
2. Animal Welfare Information Center. Alternatives and the Animal Welfare Act. <http://www.nal.usda.gov/awic/alternatives/Altbrochure.pdf>.

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Stepping on Stone

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In the past, the scientists submitted alternatives literature searches and the IACUC invariably did not question them; this is the crux of Great Eastern’s problem.

Enter Paula Stone. As the Chair of the IACUC noted, Great Eastern’s scientists will not perform more than a simple, uncomplicated review of the literature.

Given the tremendous amount of information available and the price of that information, Stone offered her expertise to assist the busy scientists in retrieving information that may have been previously unavailable to them. Although a thorough review of the literature may be relatively expensive (more than \$50), compared with the cost of animals (hamsters can cost up to \$25 each), plus per diem (23¢–\$1.50), plus veterinary support (\$100 per hour), plus miscellaneous costs, it is a minor cost and the potential benefits are great.

Stone rightfully noted that Morales’ search strategy was unlikely to retrieve information on alternatives. In fact, Morales’ search terms are too broad and general (immune system, immunity), irrelevant (alternative), or lacking (maturation, animal model – what component is actually being measured?). Additionally, because Morales searched only Medline, Stone was correct to question the adequacy of the search. A quick search of Medline, EmBase, and Biosis using the terms ‘immune system’ and ‘hamster’ found 51 citations from Medline, 79 from EmBase, and 8513 from Biosis. By any measure, it is apparent that the investigator has not made a reasonable and good faith effort to uncover alternative methods. It is also apparent, from the IACUC Chair’s treatment of Stone and the squelching of her discussion of the alternatives requirement, that the IACUC is not performing correctly under the Animal Welfare Act (AWA). In the Final Rules published in 1989, USDA APHIS stated, “We also believe that consideration of alternatives will be discussed during Committee meetings where proposed activities are presented for approval, and made part of the meeting minutes ... and the written narrative of information sources consulted will be made part of the Committee’s record¹.”

Although the IACUC may not agree with Policy 12 (ref. 2), it is the obligation of the IACUC to protect the research facility from violating the AWA. Stone has tried to use her unique background to assist the IACUC with complying with this part of the AWA, but the IACUC has dismissed her concerns as irrelevant and has intimidated

her. This may speak to a larger IACUC problem in which members are pressured to ‘go along.’

IACUCs and investigators also need to understand that identifying alternatives requires more than looking for nonanimal models. One can argue that Morales has already incorporated a refinement by using an osmotic pump, negating the need for daily restraint and injections. He should cite this in his narrative. Because most scientists perform a review of the literature for grant applications or new projects, that is the time to address the 3 Rs. The alternatives search does not have to be a separate review. This saves time and effort later, and ensures that the experiment is not unnecessarily duplicating previous work (another compliance issue). However, scientists should recognize that information may come from outside their core journals and may appear in the veterinary or laboratory animal literature, both covered by Medline (Stone was wrong about Medline), EmBase, Biosis, Agricola, CAB Abstracts (<http://www.cabi.com>), and other providers.

As part of their infrastructure, research facilities should make information resources available to enhance both compliance and research. For their part, scientists should include the cost of information in grant applications. Needless to say, in using the skills of an experienced searcher such as Stone, Morales would have had more time and useful information available for his research.

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Reference

1. USDA APHIS. Final rule. Animal welfare; final rules; 9CFR Parts 1 and 2. *Federal Register* 54, 36112–36163 (31 August 1989).
2. USDA APHIS. Animal Care Policy #12, Consideration of Alternatives to Painful/Distressful Procedures. Animal Care Resource Guide (21 June 2000). <http://www.aphis.usda.gov/ac/polmanpdf.html>.