1966 and all that—when is a literature search done?

The recent death of a 24-year-old healthy volunteer in a research study at Johns Hopkins University (see *Lancet* 2001; **358:** 2130) has highlighted many potential weaknesses in the clinical research process. One criticism made of the study, which involved volunteers inhaling hexamethonium, was the inadequacy of the literature search that underpinned the protocol. The US Office of Human Research Protections specifically noted that "the investigators and the [Hopkins] IRB failed to obtain published literature about the known association between hexamethonium and lung toxicity. Such data was readily available via routine MEDLINE and Internet database searches, as well as recent textbooks on pathology of the lung."

The pulmonary complications of hexamethonium have indeed been reported, although the cases involved varying doses and routes of administration. One article states: "During the course of treating 54 severely hypertensive patients with parenteral hexamethonium bromide, we have observed the development of unexpected pulmonary dyspnoea and associated radiographic changes in the lungs in three cases. . . . Two of these came to autopsy" (*Br Heart J* 1954; **16:** 101–08). And two articles use the term "hexamethonium lung" in their title (*J Pathol Bacteriol* 1962; **83:** 159–64 and *J Obstet Gynaecol Brit Emp* 1956; **63:** 728–34). How were these articles missed? The answer, it seems, is that all were published before 1966. As a result, none appears in a search of the PubMed database of the US National Library of Medicine.

PubMed includes MEDLINE, which covers citations to articles dating back to the mid-1960s. A separate database, OLDMEDLINE, contains citations from roughly 1958–1965. Older citations are being added at a rate of approximately 1–2 years' worth per fiscal year. While most librarians are aware of OLDMEDLINE, many researchers may not be. Sheldon Kotzin, executive editor of MEDLINE, said that separate databases exist because of different original indexing standards. Older papers had many fewer subject headings, which do not correspond to currently used terms, and they have no abstracts. Kotzin told *The Lancet* that the Hopkins case has provided renewed interest in making OLDMEDLINE accessible through PubMed.

But, as Nancy Roderer, a Hopkins librarian, pointed out, simply having the citation is useless if the actual article cannot be obtained. Furthermore, researchers ideally need to use an iterative search process, first examining indexed databases and free-text searches, studying the resulting papers, and then refining their searches, for optimal retrieval. This time-consuming task is necessitated by the "inverse relation between recall and precision", Roderer says: comprehensive retrieval is increasingly likely, but the results may include papers not precisely on the mark. Roderer recommends that researchers collaborate with a librarian if they have problems with a search, or if they need a comprehensive retrieval.

There's more to searching than surfing

"I suspect that scientific papers published before 1966 and those published before 1066 are cited with about equal regularity"

Carol G Jenkins, president of the US Medical Library Association (MLA), said that the Hopkins case underscores "the complexity of finding and evaluating biomedical literature . . . [and] the need for utilising the expertise of medical librarians". The MLA is recommending that guidelines or standards for literature searching be developed to help IRBs assess literature searches in studies they are evaluating.

Hopkins itself has already appointed a committee to develop such standards. Chi Van Dang, Hopkins' vice-dean for research, told *The Lancet* that the committee, which includes a scientist, two librarians, a pharmacologist, an expert on pharmacy databases, and two external experts, is charged with developing guidelines that can be used by both researchers and IRBs. The committee is expected to release a draft document on Sept 15.

Neuroscientist Douglas S DeWitt (University of Texas Medical Branch, Galveston, TX, USA) observed that it is all too easy to assume that MEDLINE encompasses the whole of the medical literature. "I suspect", he said, "that scientific papers published before 1966 and those published before 1066 are cited with about equal regularity."

Eugene Garfield, who pioneered many aspects of bibliometrics, including citation analysis, and founded the Institute for Scientific Information (Philadelphia, PA, USA), agreed that "the older literature is frequently overlooked". Using the Science Citation Index, which contains citations older than those in MEDLINE, he produced a list of papers that had cited the 1954 *British Heart Journal* paper. The paper has been cited by 68 other papers, and as recently as April, 2000, suggesting that citation indexes may provide yet another important dimension of literature searching.

Following these chains of citation is a way of discovering associations and trends in research over time, a kind of browsing endorsed by many researchers. Jan Vandenbroucke (University of Leiden, the Netherlands), remarked on the importance of browsing "around" old references, not only in similar papers but also in correspondence. The older literature can also be a key to discovering new ways to investigate diseases and finding "old clinical truths". "The value", he said, "is mainly scholarly, and leads to humility: when reading first descriptions of disease, or of mechanisms or of therapy, one often realises how much was already known in that first description."

The hexamethonium case at Johns Hopkins is not the first to highlight the value of the older medical literature. The thalidomide disaster that occurred in the 1950s and 1960s raised similar issues. As researchers discover new uses for old drugs—as in the current test of the 1940s malaria drug quinacrine for variant Creutzfeldt-Jacob disease (see *Lancet* 2001; **358:** 563)—it seems certain that new questions that might be answered in the old literature will continue to arise.

Faith McLellan