

TESTING TREATMENTS

Chapter 8, 8.3.3 ALL THE RELEVANT, RELIABLE EVIDENCE

continue to be commissioned and allowed to do studies that involve withholding treatments known to be effective. For example, long after reliable evidence was available showing that giving antibiotics to patients having bowel surgery reduced their chances of dying from complications of the operation, researchers continued to do comparison studies that involved withholding antibiotics from half the patients participating in controlled trials. The researchers' failure to review systematically what was already known deprived half the participants in their studies of a known beneficial treatment. This serious lapse was evidently overlooked by the funding bodies who financed their research, and by the research ethics committees which reviewed the protocols and failed to challenge the researchers.

It is not only patients requiring treatment who can be put at risk if researchers do not assess systematically what is already known about the effects of the treatments they will be given. Healthy volunteers can be harmed too. The first phase of testing some treatments often involves a very small number of healthy volunteers. In 2006, six young men volunteers at a private research facility in West London were given infusions of a drug that had not previously been used in people. They all suffered life-threatening complications – one of them losing fingers and toes – and their long-term health has been compromised. This tragedy could most probably have been avoided¹³ if a report of a severe reaction to a similar drug had been submitted for publication,¹⁴ and if the researchers had assessed systematically what was already known about the effects of such drugs.¹⁵ Had they done so, they might not have proceeded with their study at all, or if they had decided to go ahead, they might have injected the volunteers one at a time rather than simultaneously; and they could and should have warned the healthy young volunteers about the possible dangers.¹⁶

Wasted resources in healthcare and research

Failure to do systematic reviews of relevant, reliable research evidence does harm even when it is not harming patients and people participating in research. This is because it can result in resources being wasted in healthcare and health research. During

COULD CHECKING THE EVIDENCE FIRST HAVE PREVENTED A DEATH?

'In a tragic situation that could have been averted, Ellen Roche, a healthy, 24-year-old volunteer in an asthma study at Johns Hopkins University, died in June [2001] because a chemical she had been asked to inhale led to the progressive failure of her lungs and kidneys. In the aftermath of this loss, it would appear that the researcher who conducted the experiment and the ethics panel that approved it allegedly overlooked numerous clues about the dangers of the chemical, hexamethonium, given to Roche to inhale. Adding particular poignancy to the case is that evidence of the chemical's dangers could easily have been found in the published literature. *The Baltimore Sun* concluded that while the supervising physician, Dr. Alkis Togias, made "a good-faith effort" to research the drug's adverse effects, his search apparently focused on a limited number of resources, including PubMed, which is searchable only back to 1966. Previous articles published in the 1950s, however, with citations in subsequent publications, warned of lung damage associated with hexamethonium.'

Perkins E. Johns Hopkins Tragedy. *Information Today* 2001;18:51-4.

the 1980s and 1990s, for example, a total of more than 8,000 patients participated in several tests of a proposed new drug for stroke. Dutch researchers reviewed the results of these drug studies systematically, and were unable to find any beneficial effects (see Chapter 10, p121).¹⁷ They then decided to review the results of tests of the drug done previously in animals; again, they were unable to find any beneficial effects.¹⁸ Had the researchers who did the tests in animals and the clinical researchers reviewed the results of the animal studies systematically, as they had emerged, it is very likely that thousands of patients would not have been invited to participate in the clinical trials. Indeed, this might have resulted in better use of resources for treating patients experiencing stroke, and studies

that were more likely to be relevant to identifying improvements in treatments for the condition. And this is far from an isolated example.¹⁹

REPORTS OF NEW RESEARCH SHOULD BEGIN AND END WITH SYSTEMATIC REVIEWS

The report of a study²⁰ to assess the effects of giving steroids to people with acute traumatic brain injury shows how to address all of Bradford Hill's four questions. The researchers explained that they had embarked on the study because their systematic review of all the existing evidence, as well as evidence of variations in clinical use of the treatment, showed that there was important uncertainty about the effects of this widely used treatment. They reported that they had registered and published the protocol for

INSTRUCTIONS TO AUTHORS TO PUT RESEARCH RESULTS IN CONTEXT BY THE EDITORS OF THE MEDICAL JOURNAL *THE LANCET*

Systematic Review

This section should include a description of how authors searched for all the evidence. Authors should also say how they assessed the quality of that evidence – ie, how they selected and how they combined the evidence.

Interpretation

Authors should state here what their study adds to the totality of evidence when their study is added to previous work.

'We ask that all research reports – randomised or not – submitted from Aug 1 . . . put the results into the context of the totality of evidence in the Discussion.'

Clark S, Horton R. Putting research in context – revisited. *Lancet* 2010;376:10–11.