deliberately ignore existing evidence. They design, analyze, and report research to paint their own results for a particular treatment in a favourable light. This is what happened in the 1990s when the manufacturer of the anti-depressant drug Seroxat (paroxetine) withheld important evidence suggesting that, in adolescents, the drug actually increased symptoms that prompted some of these young patients to contemplate suicide as a way of dealing with their depression.⁹

Over-reporting is a problem as well. In a phenomenon known as ‘salami slicing’, researchers take the results from a single trial (the salami) and slice the results into several reports without making clear that the individual reports are not independent studies. In this way, a single ‘positive’ trial can appear in several journals in different articles, thereby introducing a bias.¹⁰ Here again, registering trials at inception with unique identifiers for every study will help to reduce the confusion that can result from this practice.

WHAT CAN HAPPEN IF ALL THE RELEVANT, RELIABLE EVIDENCE IS NOT ASSESSED?

Fair tests of treatments involve reviewing systematically all the relevant, reliable evidence, to see what is already known, whether from animal or other laboratory research, from the healthy volunteers on whom new treatments are sometimes tested, or from previous research involving patients. If this step is overlooked, or done badly, the consequences can be serious – patients in general, as well as participants in research, may suffer and sometimes die unnecessarily, and precious resources both for healthcare and for research will be squandered.

Avoidable harm to patients
Recommended treatments for heart attacks that had appeared in textbooks published over a period of 30 years were compared with evidence that could have been taken into account had the authors systematically reviewed the results of fair tests of treatment reported during that time.¹¹ This comparison showed that the textbook recommendations were often wrong because the authors

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had not reviewed the relevant evidence systematically. The impact of this was devastating. In some cases, patients with heart attacks were being deprived of life-saving therapies (for example, clot-busting drugs). In other cases, doctors continued to recommend treatments long after fair tests had shown they were lethal (for example, the use of drugs that reduce heart rhythm abnormalities in patients having heart attacks (see above and Chapter 2, p14-15).

The failure to combine the results of studies in systematic reviews as new evidence becomes available continues to harm patients. Blood substitutes that need no refrigeration or cross-matching are an obviously attractive alternative to real blood for the treatment of haemorrhage. Unfortunately these products increase the risk of heart attacks and death. Furthermore, a systematic review of the randomized trials reported since the late 1990s reveals that their dangers could and should have been recognized several years earlier than they were.¹

Avoidable harm to people participating in research
Failure to assess all relevant, reliable evidence can also result in avoidable harm to people who participate in research. Researchers

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 avoided if a report of a severe reaction to a similar drug had been submitted for publication, and if the researchers had assessed systematically what was already known about the effects of such drugs. 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.

**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.’


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). 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. 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.\textsuperscript{19}

REPORTS OF NEW RESEARCH SHOULD BEGIN AND END WITH SYSTEMATIC REVIEWS

The report of a study\textsuperscript{20} 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.’