

# TESTING TREATMENTS

## Chapter 10, 10.4 TESTING TREATMENTS

had been published. Between 1987 and 2002, the proportion of relevant previous reports cited in successive reports of aprotinin trials fell from a high of 33% to only 10% among the most recent reports. Only 7 of 44 subsequent reports referenced the report of the largest trial (which was 28 times larger than the median trial size); and none of the reports referenced systematic reviews of these trials published in 1994 and 1997.

As the authors of the analysis emphasized, science is meant to be cumulative, but many scientists are not accumulating evidence scientifically. Not only are most new studies not designed in the light of systematic reviews of existing evidence but also new evidence is only very rarely reported in the context of updates of those reviews (see Chapter 8).

### DISTORTED RESEARCH PRIORITIES

For most of the organizations supporting biomedical research and most of the researchers doing it, their stated aim is straightforward: to contribute information to improve people's health. But how many of the millions of biomedical research reports published every year really do make a useful contribution to this worthy cause?

#### Questions that are important for patients

Researchers in Bristol decided to pose a fundamental question: 'To what extent are questions of importance to patients with osteoarthritis of the knee and the clinicians looking after them reflected in the research on this condition?'<sup>17</sup> They began by convening four focus groups – of patients, rheumatologists, physiotherapists, and general practitioners, respectively. These groups were unanimous in making clear that they did not want any more trials sponsored by pharmaceutical companies comparing yet another non-steroidal anti-inflammatory drug (the group of drugs that includes, for example, ibuprofen) against a placebo. Instead of drug trials, patients wanted rigorous evaluation of physiotherapy and surgery, and assessment of the educational and coping strategies that might help patients to manage this chronic, disabling, and often painful condition more successfully.

Of course, these forms of treatment and management offer much less scope than drugs for commercial exploitation, and so are often ignored.

How many other fields of therapeutic research would, if evaluated in this way, reveal similar mismatches between the questions about treatment effects that matter to patients and clinicians, and those that researchers are addressing? Regrettably, mismatch appears to be the rule rather than the exception.<sup>18, 19, 20, 21</sup>

Minor changes in drug formulation rarely lead to the drugs having substantially new, more useful effects, yet these types of studies dominate research into treatments not only for arthritis but also for other chronic disorders. What a waste of resources!

### **Who decides what gets studied?**

Clearly this situation is unsatisfactory, so how has it come about? One reason is that what gets studied by researchers is distorted by external factors.<sup>22</sup> The pharmaceutical industry, for example, does research for its primary need – to fulfil its overriding responsibility to shareholders to make a profit. Its responsibility to patients and clinicians comes second. Businesses are driven by large markets – such as women wondering whether to use hormone replacement therapy, or people who are depressed, anxious, unhappy, or in pain. Yet only rarely in recent decades has this commercially targeted approach led to important new treatments, even for ‘mass market’ disorders. Rather, within groups of drugs, industry has usually produced many very similar compounds – so-called ‘me-too’ drugs. This is reminiscent of the days when the only bread available in supermarkets was endless variations on the white sliced loaf. Hardly surprising, then, that the pharmaceutical industry spends more on marketing than on research.

But how does industry persuade prescribers to use these new products rather than existing, less expensive alternatives? A common strategy is to commission numerous small research projects showing that the new drugs are better than giving nothing at all, while not doing any research to find out whether the new drugs are better than the existing ones. Regrettably, industry has little difficulty in finding doctors who are willing to enrol their patients in this fruitless enterprise. And the same doctors often

### IMPACT OF 'ME-TOO' DRUGS IN CANADA

'In British Columbia most (80%) of the increase in drug expenditure between 1996 and 2003 was explained by the use of new, patented drug products that did not offer substantial improvements on less expensive alternatives available before 1990. The rising cost of using these me-too drugs at prices far exceeding those of time tested competitors deserves careful scrutiny. Approaches to drug pricing such as those used in New Zealand may enable savings that could be diverted towards other healthcare needs. For example, \$350m (26% of total expenditure on prescription drugs) would have been saved in British Columbia if half of the me-too drugs consumed in 2003 were priced to compete with older alternatives. This saving could pay the fees of more than a thousand new doctors.

Given that the list of top 20 drugs in global sales includes newly patented versions of drugs in long established categories . . . me-too drugs probably dominate spending trends in most developed countries.'

Morgan SG, Bassett KL, Wright JM, *et al.* 'Breakthrough' drugs and growth in expenditure on prescription drugs in Canada. *BMJ* 2005;331:815-6.

end up prescribing the products studied in this way.<sup>23</sup> Moreover, drug licensing authorities often make the problem worse by insisting that new drugs should be compared with placebos, rather than with existing effective treatments.

Another strategy is ghostwriting. This is what happens when a professional writer writes text that is officially credited to someone else. Most people will have come across 'celebrity autobiographies' that have clearly been 'ghosted' in this way. However, ghostwritten material appears in academic publications too – and with potentially worrying consequences. Sometimes the pharmaceutical industry employs communication companies to prepare articles which, unsurprisingly, cast the industry's product in a favourable light. Once the article is ready, an academic is

## DOCTORS AND DRUG COMPANIES

‘No one knows the total amount provided by drug companies to physicians, but I estimate from the annual reports of the top nine US drug companies that it comes to tens of billions of dollars a year. By such means, the pharmaceutical industry has gained enormous control over how doctors evaluate and use its own products. Its extensive ties to physicians, particularly senior faculty at prestigious medical schools, affect the results of research, the way medicine is practiced, and even the definition of what constitutes a disease.’

Angell M. *Drug companies & doctors: a story of corruption*.  
New York Review of Books, January 15, 2009.

signed up, for an ‘honorarium’, to ‘author’ it. Then the article is submitted for publication. Commentaries are especially popular for this purpose. Industry also targets journal supplements – separately bound publications that, while carrying the name of the parent journal, are often sponsored by industry and tend not to be as rigorously peer-reviewed as the parent journal.<sup>24</sup> Marketing messages created and promoted in ways such as these have led to the benefits of products being oversold and harms being downplayed (see also Chapter 8, p97).

Drug companies also place adverts in medical journals to promote their products. Typically these adverts include references to sources of evidence to back the claims being made. These may be convincing at first glance, but a different picture emerges when the evidence is scrutinized independently. Even when the evidence comes from randomized trials – which those reading the adverts might well assume to be a reliable assessment – all is not as it seems. When researchers analyzed adverts in leading medical journals to see whether the randomized trial evidence stacked up, they found that only 17% of the trials referenced were of good quality, supported the claim being made for the drug in question, and were not sponsored by the drug company itself. And it is known that research sponsored in this way is more likely

### DODGY, DEVIOUS, AND DUPED?

Writing a light-hearted article for a Christmas edition of the *British Medical Journal*, two researchers created a spoof company called HARLOT plc to provide a series of services for trial sponsors. For example:

‘We can guarantee positive results for the manufacturers of dodgy drugs and devices who are seeking to increase their market shares, for health professional guilds who want to increase the demand for their unnecessary diagnostic and therapeutic services, and for local and national health departments who are seeking to implement irrational and self-serving health policies. . . for dodgy “me too” drugs [our E-Zee-Me-Too Protocol team] can guarantee you a positive trial.’

To their astonishment, the authors received some apparently serious inquiries about the amazing HARLOT plc portfolio.

Sackett DL, Oxman AD. HARLOT plc: an amalgamation of the world's two oldest professions. *BMJ* 2003;327:1442-5.

to find a favourable outcome for the company's product.<sup>25, 26</sup>

Commentaries in prestigious medical journals such as *The Lancet*<sup>27</sup> have drawn attention to the perverse incentives now driving some of those involved in clinical research, and the increasingly dubious relationships between universities and industry. A former editor of the *New England Journal of Medicine* asked bluntly ‘Is academic medicine for sale?’<sup>28</sup>

Commercial priorities are not the only perverse influences on patterns of biomedical research which ignore the interests of patients. Many people within universities and research funding organizations believe that improvements in health are most likely to stem from attempts to unravel basic mechanisms of disease. So, they do research in laboratories and with animals. Although such basic research is unquestionably needed, there is precious little evidence to support its substantially greater share of funding

**ALL IT TAKES IS TO FIND THE GENE**

‘It’s . . . hoped that the genetic revolution will cure every problem known to man. We will be able to locate and replicate the genes that predispose us towards building better housing, eliminating pollution, enduring cancer more bravely, implementing funds for universally available child-care facilities, and agreeing on the location and design of a national sports stadium. Soon, every newborn will be delivered on to a genetically level playing field. The gene that, say, makes girls do better at GCSEs [high school exams] than boys will be identified and removed. The genetic possibilities are endless. . . . So, yes we’re entering an uncertain world, but one that holds out certain hope. For whatever the grave moral quandaries the genetic issue throws up, it will one day be possible to isolate the gene that solves them.’

Iannucci A. *The Audacity of Hype*. London: Little, Brown, 2009, pp270-1

than research involving patients.<sup>29, 30</sup> Yet the consequence has been a massive outpouring of laboratory research that has not been properly evaluated to see how relevant it is to patients.

One reason for this distortion is the hype surrounding the hoped-for clinical advances that basic research, especially genetics, might offer (see Chapter 4, p43-44 for genetic tests). Yet, as Sir David Weatherall, a distinguished clinician and genetics researcher, observed in 2011, ‘Many of our major killers reflect the action of a large number of genes with small effects, combined with a major input from the physical and social environment. This work is producing valuable information about some disease processes, but it also emphasises the individuality and variability of the underlying mechanisms of diseases. Clearly, the era of personalised medicine based on our genetic makeup is a long way in the future.’<sup>31</sup>

Now, over fifty years after the structure of DNA was discovered, the cacophony of claims about early healthcare benefits of the ‘genetic revolution’ seems to be diminishing. Reality is starting to set in. One scientist, talking about the potential for genetics to

## PSORIASIS PATIENTS POORLY SERVED BY RESEARCH

'Few trials involved comparison of different options or looked at long-term management. The duration of studies is unconvincingly brief in the context of a disease of potentially near life-long chronicity. We seem to know reliably only that our treatments are better than nothing at all. Tellingly, researchers have completely ignored patient experience, views, preferences, or satisfactions.'

R Jobling, Chairman, Psoriasis Association

Jobling R. Therapeutic research into psoriasis: patients' perspectives, priorities and interests. In: Rawlins M, Littlejohns P, eds. *Delivering quality in the NHS 2005*. Abingdon: Radcliffe Publishing Ltd, pp53-56.

result in development of new drugs, commented 'We have moved into an era of realism. . . . genetic aspects have to be looked at in association with other factors including environment and the clinical use of drugs. Just because a drug doesn't work in a patient doesn't indicate genetic variation in response is the cause.'<sup>32</sup> And an editorial in the science journal *Nature*, in an issue celebrating the tenth anniversary of the sequencing of the human genome, noted ' . . . there has been some progress, in the form of drugs targeted against specific genetic defects identified in a few types of cancer, for example, and in some rare inherited disorders. But the complexity of post-genome biology has dashed early hopes that this trickle of therapies would become a flood.'<sup>33</sup>

There is simply no way of bypassing responsibly the need for well-designed research in patients to test the therapeutic theories derived from basic research. And, all too often, such theories are never followed through to see if they do have any relevance for patients. More than two decades after researchers identified the genetic defect leading to cystic fibrosis, people with the condition are still asking a fundamental question. When will they see dividends to their health resulting from the discovery?

Even when research may seem relevant to patients, researchers

often appear to overlook patients' concerns when they design their studies. In a telling illustration, lung cancer doctors were asked to put themselves in the position of patients and to consider whether they would consent to participate in each of six lung cancer trials for which they might, as patients, be eligible. Between 36 and 89 per cent of them said that they would *not* participate.<sup>34</sup>

Similarly, in clinical trials in psoriasis – a chronic and disabling skin condition that affects about 125 million people worldwide – patients' interests have been poorly represented.<sup>35, 36</sup> For example, the Psoriasis Association in the UK found that researchers persisted in using a largely discredited scoring system in many studies to assess the effects of various treatments. Among its deficiencies, the scoring system concentrates on measures such as total area of skin affected and thickness of the lesions, whereas patients, not surprisingly, are more troubled by lesions on the face, palms and soles, and genitals.<sup>37</sup>

### KEY POINTS

- Unnecessary research is a waste of time, effort, money, and other resources; it is also unethical and potentially harmful to patients
- New research should only proceed if an up-to-date review of earlier research shows that it is necessary, and after it has been registered
- Evidence from new research should be used to update the previous review of all the relevant evidence
- Much research is of poor quality and done for questionable reasons
- There are perverse influences on the research agenda, from both industry and academia
- Questions that matter to patients are often not addressed