how to

READ A PAPER

the basics of evidence-based medicine

FOURTH EDITION

Trisha Greenhalgh

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Table of Contents

In November 1995, my friend Ruth Holland, book reviews editor of the British Medical Journal, suggested that I write a book to demystify the important but often inaccessible subject of evidence-based medicine. She provided invaluable comments on earlier drafts of the manuscript, but was tragically killed in a train crash on 8th August 1996. This book is dedicated to her memory.

How to Read a Paper

The basics of evidence-based medicine

FOURTH EDITION

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This edition first published 2010 © 2010 by Patricia Greenhalgh

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Registered office: John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK

Editorial offices: 9600 Garsington Road, Oxford, OX4 2DQ, UK

The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK

111 River Street, Hoboken, NJ 07030-5774, USA

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Library of Congress Cataloging-in-Publication Data

Greenhalgh, Trisha.

How to read a paper : the basics of evidence-based medicine / Trisha Greenhalgh. – 4th ed.

p.; cm.

Includes bibliographical references and index.

ISBN 978–1–4443–3436–4

1. Medical literature—Evaluation. 2. Medicine—Research—Evaluation. 3. Evidence-based medicine. I. Title. [DNLM: 1. Evidence-Based Practice. 2. Journalism, Medical. 3. Research. WB 102.5 G813h 2010]

R118.6.G74 2010

610.72—dc22

2009051037

A catalogue record for this book is available from the British Library.

Foreword to the First Edition by Professor Sir David Weatherall

Not surprisingly, the wide publicity given to what is now called “evidence-based medicine” has been greeted with mixed reactions by those who are involved in the provision of patient care. The bulk of the medical profession appears to be slightly hurt by the concept, suggesting as it does that until recently all medical practice was what Lewis Thomas has described as a frivolous and irresponsible kind of human experimentation, based on nothing but trial and error, and usually resulting in precisely that sequence. On the other hand, politicians and those who administrate our health services have greeted the notion with enormous glee. They had suspected all along that doctors were totally uncritical and now they had it on paper. Evidence-based medicine came as a gift from the gods because, at least as they perceived it, its implied efficiency must inevitably result in cost saving.

The concept of controlled clinical trials and evidence-based medicine is not new however. It is recorded that Frederick II, Emperor of the Romans and King of Sicily and Jerusalem, who lived from 1192 to 1250 AD, and who was interested in the effects of exercise on digestion, took two knights and gave them identical meals. One was then sent out hunting and the other ordered to bed. At the end of several hours he killed both and examined the contents of their alimentary canals; digestion had proceeded further in the stomach of the sleeping knight. In the 17th century Jan Baptista van Helmont, a physician and philosopher, became sceptical of the practice of blood-letting. Hence he proposed what was almost certainly the first clinical trial involving large numbers, randomisation and statistical analysis. This involved taking 200 to 500 poor people, dividing them into two groups by casting lots, and protecting one from phlebotomy while allowing the other to be treated with as much blood-letting as his colleagues thought appropriate. The number of funerals in each group would be used to assess the efficacy of blood-letting. History does not record why this splendid experiment was never carried out.

If modern scientific medicine can be said to have had a beginning it was in Paris in the mid-19th century and where it had its roots in the work and teachings of Pierre Charles Alexandre Louis. Louis introduced statistical analysis to the evaluation of medical treatment and, incidentally, showed that blood-letting was a valueless form of treatment, though this did not change the habits of the physicians of the time, or for many years to come. Despite this pioneering work few clinicians on either side of the Atlantic urged that trials of clinical outcome should be adopted, although the principles of numerically-based experimental design were enunciated in the 1920s by the geneticist Ronald Fisher. The field only started to make a major impact on clinical practice after the Second World War following the seminal work of Sir Austin Bradford Hill and the British epidemiologists who followed him, notably Richard Doll and Archie Cochrane.

But although the idea of evidence-based medicine is not new, modern disciples like David Sackett and his colleagues are doing a great service to

clinical practice, not just by popularising the idea but by bringing home to clinicians the notion that it is not a dry academic subject but more a way of thinking that should permeate every aspect of medical practice. While much of it is based on mega-trials and meta-analyses it should also be used to influence almost everything that a doctor does. After all, the medical profession has been brain-washed for years by examiners in medical schools and Royal Colleges to believe that there is only one way of examining a patient. Our bedside rituals could do with as much critical evaluation as our operations and drug regimes; the same goes for almost every aspect of doctoring.

As clinical practice becomes busier, and time for reading and reflection becomes even more precious, the ability effectively to peruse the medical literature and, in the future, to become familiar with a knowledge of best practice from modern communication systems, will be essential skills for doctors. In this lively book Trisha Greenhalgh provides an excellent approach to how to make best use of medical literature and the benefits of evidence-based medicine. It should have equal appeal for first year medical students and grey-haired consultants, and deserves to be read widely.

With increasing years the privilege of being invited to write a foreword to a book by one's ex-students becomes less of a rarity. Trisha Greenhalgh was the kind of medical student who never let her teachers get away with a loose thought and this inquiring attitude seems to have flowered over the years; this is a splendid and timely book and I wish it all the success it deserves. After all, the concept of evidence-based medicine is nothing more than the state of mind that every clinical teacher hopes to develop in their students; Dr Greenhalgh's sceptical but constructive approach to medical literature suggests that such a happy outcome is possible at least once in the lifetime of a professor of medicine.

D. J. Weatherall

Oxford, September 1996

Preface to the First Edition: do you need to read this book?

This book is intended for anyone, whether medically qualified or not, who wishes to find their way into the medical literature, assess the scientific validity and practical relevance of the articles they find, and, where appropriate, put the results into practice. These skills constitute the basics of evidence-based medicine.

I hope this book will help you to read and interpret medical papers better. I hope, in addition, to convey a further message, which is this. Many of the descriptions given by cynics of what evidence-based medicine is (the glorification of things that can be measured without regard for the usefulness or accuracy of what is measured, the uncritical acceptance of published numerical data, the preparation of all-encompassing guidelines by self-appointed "experts" who are out of touch with real medicine, the debasement of clinical freedom through the imposition of rigid and dogmatic clinical protocols, and the over-reliance on simplistic, inappropriate, and often incorrect economic analyses) are actually criticisms of what the evidence-based medicine movement is fighting *against*, rather than of what it represents.

Do not, however, think of me as an evangelist for the gospel according to evidence-based medicine. I believe that the science of finding, evaluating and implementing the results of medical research can, and often does, make patient care more objective, more logical, and more cost-effective. If I didn't believe that, I wouldn't spend so much of my time teaching it and trying, as a general practitioner, to practise it. Nevertheless, I believe that when applied in a vacuum (that is, in the absence of common sense and without regard to the individual circumstances and priorities of the person being offered treatment or to the complex nature of clinical practice and policymaking), 'evidence-based' decision-making is a reductionist process with a real potential for harm.

Finally, you should note that I am neither an epidemiologist nor a statistician, but a person who reads papers and who has developed a pragmatic (and at times unconventional) system for testing their merits. If you wish to pursue the epidemiological or statistical themes covered in this book, I would encourage you to move on to a more definitive text, references for which you will find at the end of each chapter.

Trisha Greenhalgh

November 1996

Preface to the Fourth Edition

When I wrote this book in 1996, evidence-based medicine was a bit of an unknown quantity. A handful of academics (including me) were already enthusiastic and had begun running 'training the trainers' courses to disseminate what we saw as a highly logical and systematic approach to clinical practice. Others – certainly the majority of clinicians – were convinced that this was a passing fad that was of limited importance and would never catch on. I wrote *How to Read a Paper* for two reasons. First, students on my own courses were asking for a simple introduction to the principles presented in what was then known as "Dave Sackett's big red book" (Sackett DL, Haynes RB, Guyatt GH, Tugwell P. Clinical Epidemiology – a basic science for clinical medicine. London, Little, Brown & Co., 1991) – an outstanding and inspirational volume that was already in its fourth reprint, but which some novices apparently found a hard read. Second, it was clear to me that many of the critics of evidence-based medicine didn't really understand what they were dismissing – and that until they did, serious debate on the political, ideological and pedagogical place of evidence-based medicine as a discipline could not begin.

I am of course delighted that *How to Read a Paper* has become a standard reader in many medical and nursing schools, and that it has so far been translated into French, German, Italian, Spanish, Portuguese, Chinese, Polish, Japanese, Czech and Russian. I am also delighted that what was so recently a fringe subject in academia has been well and truly mainstreamed in clinical service. In the UK, for example, it is now a contractual requirement for all doctors, nurses and pharmacists to practise (and for managers to manage) according to best research evidence.

In the 14 years since the first edition of this book was published, evidence-based medicine has waxed and waned in popularity. Some 700 textbooks and 25,000 journal articles now offer different angles on the 'basics of EBM' covered briefly in the chapters that follow. An increasing number of these sources point out genuine limitations of evidence-based medicine in certain contexts. Others look at evidence-based medicine as a social movement – a 'bandwagon' that took off at a particular time (the 1990s) and place (north America) and spread dramatically quickly with all sorts of knock-on effects for particular interest groups.

When preparing this fourth edition, I was advised by my publisher not to change too much, since there is clearly still room on the bookshelves for a no-frills introductory text. Many of the chapters are essentially unchanged apart from adding illustrations and updating the reference lists. Some chapters – notably those on searching, qualitative research, systematic review, and implementing evidence-based practice – have been substantially revised because the fields have moved on significantly since the previous edition. I am particularly indebted to Jeanette Buckingham from the University of Alberta, Canada for writing the lion's share of Chapter 2 on Searching the Literature. I first met Jeanette on one of the week-long Evidence Based Medicine Workshops in the late 1990s. A librarian by background, she has many years' experience of teaching EBM to medical students and doctors, and she is one

of the first people I go to when I'm foxed with a search query myself. I've also added two new chapters – on quality improvement and complex interventions. As ever, I would welcome any feedback that will help make the text more accurate, readable and practical.

Trisha Greenhalgh

January 2010

Acknowledgements

I am not by any standards an expert on all of the subjects covered in this book (in particular, I am very bad at sums), and I am grateful to the people listed below for help along the way. I am, however, the final author of every chapter, and responsibility for any inaccuracies is mine alone.

1 To Professor Sir Andy Haines and Professor Dave Sackett who introduced me to the subject of evidence-based medicine and encouraged me to write about it.

2 To the late Dr Anna Donald, who broadened my outlook through valuable discussions on the implications and uncertainties of this evolving discipline.

3 To Jeanette Buckingham of the University of Alberta, Canada, for invaluable input to Chapter 2.

4 To various expert advisers and proofreaders who had direct input to this new edition or who advised me on previous editions.

5 To the many readers, too numerous to mention individually, who took time to write in and point out both typographical and factual errors in previous editions. As a result of their contributions, I have learnt a great deal (especially about statistics) and the book has been improved in many ways. Some of the earliest critics of *How to Read a Paper* have subsequently worked with me on my teaching courses in evidence-based practice; several have co-authored other papers or book chapters with me, and one or two have become personal friends.

6 To various colleagues, named in the different chapters, who gave permission for me to reproduce figures and tables. Box 2 of chapter 11, reproduced from Tony Hope and colleagues' book *Medical Ethics and Law: The Core Curriculum*, is based on data provided by Dr A Briggs and Professor A Gray, Department of Public Health, University of Oxford.

Thanks also to my husband, Dr Fraser Macfarlane, for his unfailing support for my academic work and writing. My sons Rob and Al had not long been born when the first edition of this book was being written. It is a source of great pride to me that they have now read the book, applied its messages in their own developing scientific careers and made suggestions for how to improve it.

Chapter 1 Why read papers at all?

1.1 Does 'evidence-based medicine' simply mean 'reading papers in medical journals'?

Evidence-based medicine (EBM) is much more than just reading papers. According to the most widely quoted definition, it is 'the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients'.[1] I find this definition useful up to a point but it misses out what for me is a very important aspect of the subject – the use of mathematics. Even if you know almost nothing about EBM you know it talks a lot about numbers and ratios. Anna Donald and I decided to be up front about this in our own teaching, and proposed this alternative definition:

> *'Evidence-based medicine is the use of mathematical estimates of the risk of benefit and harm, derived from high-quality research on population samples, to inform clinical decision-making in the diagnosis, investigation or management of individual patients.'*

The defining feature of EBM, then, is the use of figures derived from research on *populations* to inform decisions about *individuals*. This, of course, begs the question 'What is research?' – for which a reasonably accurate answer might be 'Focused, systematic enquiry aimed at generating new knowledge'. In later chapters, I will explain how this definition can help you distinguish genuine research (which should inform your practice) from the poor-quality endeavours of well-meaning amateurs (which you should politely ignore).

If you follow an evidence-based approach to clinical decision-making, therefore, all sorts of issues relating to your patients (or, if you work in public health medicine, issues relating to groups of people) will prompt you to ask questions about scientific evidence, seek answers to those questions in a systematic way and alter your practice accordingly.

You might ask questions, for example, about a patient's symptoms ('In a 34-year-old man with left-sided chest pain, what is the probability that there is a serious heart problem, and if there is, will it show up on a resting ECG?'), about physical or diagnostic signs ('In an otherwise uncomplicated childbirth, does the presence of meconium [indicating fetal bowel movement] in the amniotic fluid indicates significant deterioration in the physiological state of the fetus?'), about the prognosis of an illness ('If a previously well 2 year old has a short fit associated with a high temperature, what is the chance that she will subsequently develop epilepsy?'), about therapy ('In patients with an acute coronary syndrome [heart attack], are the risks associated with thrombolytic drugs [clotbusters] outweighed by the benefits, whatever the patient's age, sex and ethnic origin?'), about cost-effectiveness ('Is the cost of this new anti-

cancer drug justified, compared with other ways of spending limited healthcare resources?'), about patients' preferences ('In women attending a male doctor for a vaginal examination, what proportion would like to be offered a chaperone?'), and about a host of other aspects of health and health services.

Professor Dave Sackett, in the opening editorial of the very first issue of the journal *Evidence-Based Medicine* summarised the essential steps in the emerging science of EBM:[2]

1 to convert our information needs into answerable questions (i.e. to formulate the problem);

2 to track down, with maximum efficiency, the best evidence with which to answer these questions – which may come from the clinical examination, the diagnostic laboratory, the published literature or other sources;

3 to appraise the evidence critically (i.e. weigh it up) to assess its validity (closeness to the truth) and usefulness (clinical applicability);

4 to implement the results of this appraisal in our clinical practice;

5 to evaluate our performance.

Hence, EBM requires you not only to read papers, but also to read the *right* papers at the right time, and then to alter your behaviour (and, what is often more difficult, influence the behaviour of other people) in the light of what you have found. I am concerned that the plethora of how-to-do-it courses in EBM so often concentrate on the third of these five steps (critical appraisal) to the exclusion of all the others. Yet if you have asked the wrong question or sought answers from the wrong sources, you might as well not read any papers at all. Equally, all your training in search techniques and critical appraisal will go to waste if you do not put at least as much effort into implementing valid evidence and measuring progress towards your goals as you do into reading the paper. A few years ago I added three more stages to Sackett's five-stage model to incorporate the patient's perspective: the resulting eight stages, which I have called a context-sensitive checklist for evidence-based practice, are shown in Appendix 1.[3]

If I were to be pedantic about the title of this book, these broader aspects of EBM should not even get a mention here. But I hope you would have demanded your money back if I had omitted the final section of this chapter (Before you start: formulate the problem), Chapter 2 (Searching the literature) and Chapter 15 (Implementing evidence-based practice). Chapters 3–14 describe step three of the EBM process: critical appraisal – that is what you should do when you actually have the paper in front of you.

Incidentally, if you are computer-literate and want to explore the subject of EBM on the Internet, you could try the following websites. If you're not, don't worry (and don't worry either when you discover that there are over 1000 websites dedicated to EBM – they all offer very similar material and you certainly don't need to visit them all).

1 *Oxford Centre for Evidence-Based Medicine*. A well-kept website from Oxford, UK containing a wealth of resources and links for EBM. http://cebm.net

2 *Intute.* Formerly Omni, a web portal to evidence-based resources in medicine, nursing, midwifery, veterinary medicine and more. http://www.intute.ac.uk/

3 *National Institute for Health and Clinical Excellence (NICE)*. This UK-based website, which is also popular outside the UK, links to evidence-based guidelines and topic reviews. http://www.nice.org.uk/

4 *NHS Centre for Reviews and Dissemination*. The site for downloading the high-quality evidence-based reviews is part of the UK National Institute for Health Research – a good starting point for looking for evidence on complex questions such as 'what should we do about obesity?' http://www.york.ac.uk/inst/crd/

5 *Clinical Evidence*. An online version of the excellent 6-monthly handbook of best evidence for clinical decisions such as 'what's the best current treatment for atrial fibrillation?' Produced by BMJ Publishing Group http://clinicalevidence.bmj.com

1.2 Why do people sometimes groan when you mention EBM?

Critics of EBM might define it as: 'the tendency of a group of young, confident and highly numerate medical academics to belittle the performance of experienced clinicians using a combination of epidemiological jargon and statistical sleight-of-hand', or: 'the argument, usually presented with near-evangelistic zeal, that no health-related action should ever be taken by a doctor, a nurse, a purchaser of health services, or a policymaker, unless and until the results of several large and expensive research trials have appeared in print and approved by a committee of experts'.

The resentment amongst some health professionals towards the EBM movement[4] is mostly a reaction to the implication that doctors (and nurses, midwives, physiotherapists and other health professionals) were functionally illiterate until they were shown the light, and that the few who weren't illiterate wilfully ignored published medical evidence. Anyone who works face-to-face with patients knows how often it is necessary to seek new information before making a clinical decision. Doctors have spent time in libraries since libraries were invented. In general, we don't put a patient on a new drug without evidence that it is likely to work. Apart from anything else, such off-licence use of medication is, strictly speaking, illegal. Surely we have all been practising EBM for years, except when we were deliberately bluffing (using the 'placebo' effect for good medical reasons), or when we were ill, overstressed or consciously being lazy?

Well, no, we haven't. There have been a number of surveys on the behaviour of doctors, nurses and related professionals. It was estimated in the 1970s in the USA that only around 10–20% of all health technologies then available (i.e. drugs, procedures, operations and so on) were evidence based; that figure improved to 21% in 1990, according to official US statistics.[5] Studies of the interventions offered to consecutive series of patients suggested that 60–90% of clinical decisions, depending on the specialty, were 'evidence based'.[6] But as I have argued elsewhere, such studies had methodological limitations.[3] Apart from anything else, they were undertaken in

specialised units and looked at the practice of world experts in EBM; hence, the figures arrived at can hardly be generalised beyond their immediate setting (see Section 4.2). In all probability, we are still selling our patients short quite a lot of the time.

Let's take a look at the various approaches that health professionals use to reach their decisions in reality – all of which are examples of what EBM *isn't.*

Decision-making by anecdote. When I was a medical student, I occasionally joined the retinue of a distinguished professor as he made his daily ward rounds. On seeing a new patient, he would enquire about the patient's symptoms, turn to the massed ranks of juniors around the bed and relate the story of a similar patient encountered a few years previously. 'Ah, yes. I remember we gave her such-and-such, and she was fine after that'. He was cynical, often rightly, about new drugs and technologies, and his clinical acumen was second to none. Nevertheless, it had taken him 40 years to accumulate his expertise, and the largest medical textbook of all – the collection of cases that were outside his personal experience – was forever closed to him.

Anecdote (storytelling) has an important place in clinical practice.[7] Psychologists have shown that students acquire the skills of medicine, nursing and so on by memorising what was wrong with particular patients, and what happened to them, in the form of stories or 'illness scripts'. Stories about patients are the unit of analysis (i.e. the thing we study) in grand rounds and teaching sessions. Clinicians glean crucial information from patients' illness narratives – most crucially, perhaps, what being ill *means* to the patient.[8] And experienced doctors and nurses rightly take account of the accumulated 'illness scripts' of all their previous patients when managing subsequent patients. But that doesn't mean simply doing the same for patient B as you did for patient A if your treatment worked, and doing precisely the opposite if it didn't.

The dangers of decision-making by anecdote are well illustrated by considering the risk–benefit ratio of drugs and medicines. In my first pregnancy, I developed severe vomiting and was given the anti-sickness drug prochlorperazine (Stemetil). Within minutes, I went into an uncontrollable and very distressing neurological spasm. Two days later, I had recovered fully from this idiosyncratic reaction, but I have never prescribed the drug since, even though the estimated prevalence of neurological reactions to prochlorperazine is only one in several thousand cases. Conversely, it is tempting to dismiss the possibility of rare but potentially serious adverse effects from familiar drugs – such as thrombosis on the contraceptive pill – when one has never encountered such problems in oneself or one's patients.

We clinicians would not be human if we ignored our personal clinical experiences, but we would be better to base our decisions on the collective experience of thousands of clinicians treating millions of patients, rather than on what we as individuals have seen and felt. Chapter 5 of this book (Statistics for the non-statistician) describes some more objective methods, such as the number needed to treat (NNT), for deciding whether a particular drug (or other intervention) is likely to do a patient significant good or harm.

When the EBM movement was still in its infancy, Dave Sackett emphasised

that evidence-based practice was no threat to old-fashioned clinical experience or judgement.[1] The question of *how* clinicians can manage to be both 'evidence based' (i.e. systematically informing their decisions by research evidence) and 'narrative based' (i.e. embodying all the richness of their accumulated clinical anecdotes and treating each patient's problem as a unique illness story rather than as a 'case of X') is a difficult one to address philosophically, and beyond the scope of this book. The interested reader might like to look up two articles I've written on this topic.[9,10]

Decision-making by press cutting. For the first 10 years after I qualified, I kept an expanding file of papers that I had ripped out of my medical weeklies before binning the less interesting parts. If an article or editorial seemed to have something new to say, I consciously altered my clinical practice in line with its conclusions. All children with suspected urinary tract infections should be sent for scans of the kidneys to exclude congenital abnormalities, said one article, so I began referring anyone under the age of 16 with urinary symptoms for specialist investigations. The advice was in print, and it was recent, so it must surely replace what had been standard practice – in this case, referring only children below the age of 10 who had had two well-documented infections.

This approach to clinical decision-making is still very common. How many doctors do you know who justify their approach to a particular clinical problem by citing the results section of a single published study, even though they could not tell you anything at all about the methods used to obtain those results? Was the trial randomised and controlled (see Section 3.6)? How many patients, of what age, sex and disease severity, were involved (see Section 4.2)? How many withdrew from ('dropped out of') the study, and why (see Section 4.6)? By what criteria were patients judged cured see Section 6.3? If the findings of the study appeared to contradict those of other researchers, what attempt was made to validate (confirm) and replicate (repeat) them (see Section 8.3)? Were the statistical tests that allegedly proved the authors' point appropriately chosen and correctly performed (see Chapter 5)? Doctors (and nurses, midwifes, medical managers, psychologists, medical students and consumer activists) who like to cite the results of medical research studies have a responsibility to ensure that they first go through a checklist of questions like these (more of which are listed in Appendix 1).

Decision-making by GOBSAT (good old boys sat around a table). When I wrote the first edition of this book in the mid 1990s, the commonest sort of guideline was what was known as a consensus statement – the fruits of a weekend's hard work by a dozen or so eminent experts who had been shut in a luxury hotel, usually at the expense of a drug company. Such 'GOBSAT guidelines' often fell out of the medical freebies (free medical journals and other 'information sheets' sponsored directly or indirectly by the pharmaceutical industry) as pocket-sized booklets replete with potted recommendations and at-a-glance management guides. But who says the advice given in a set of guidelines, a punchy editorial or an amply-referenced overview is correct?

Professor Cynthia Mulrow, one of the founders of the science of systematic review (see Chapter 9), showed a few years ago that experts in a particular

clinical field are *less* likely to provide an objective review of all the available evidence than a non-expert who approaches the literature with unbiased eyes.[11] In extreme cases, an 'expert opinion' may consist simply of the lifelong bad habits and personal press cuttings of an ageing clinician, and a gaggle of such experts would simply multiply the misguided views of any one of them. Table 1.1 gives examples of practices that were at one time widely accepted as good clinical practice (and which would have made it into the GOBSAT guideline of the day), but which have subsequently been discredited by high-quality clinical trials.

Chapter 9 of the book takes you through a checklist for assessing whether a 'systematic review of the evidence' produced to support recommendations for practice or policymaking really merits the description, and Chapter 10 discusses the harm that can be done by applying guidelines that are not evidence based. It is a major achievement of the EBM movement that almost no guideline these days is produced by GOBSAT.

Decision-making by cost-minimisation. Lay people are usually horrified when they learn that a treatment has been withheld from a patient for reasons of cost. Managers, politicians, and, increasingly, doctors, can count on being pilloried by the press when a child with a rare cancer is not sent to a specialist unit in America or a frail old lady is denied a drug to stop her visual loss from macular degeneration. Yet in the real world, all health care is provided from a limited budget and it is increasingly recognised that clinical decisions must take into account the economic costs of a given intervention. As Chapter 11 argues, clinical decision-making *purely* on the grounds of cost ('cost-minimisation' – purchasing the cheapest option with no regard to how effective it is) is generally ethically unjustified, and we are right to object vocally when this occurs.

Expensive interventions should not, however, be justified simply because they are new, or because they ought to work in theory, or because the only alternative is to do nothing – but because they are very likely to save life or significantly improve its quality. How, though, can the benefits of a hip replacement in a 75 year old be meaningfully compared with that of cholesterol-lowering drugs in a middle-aged man or infertility investigations for a couple in their twenties? Somewhat counter-intuitively, there is no self-evident set of ethical principles or analytical tools that we can use to match limited resources to unlimited demand. As you will see in Chapter 11, the much-derided quality-adjusted life year (QALY), and similar utility-based units are simply attempts to lend some objectivity to the illogical but unavoidable comparison of apples with oranges in the field of human suffering. In the UK, the National Institute for Health and Clinical Excellence (see www.nice.org.uk) seeks to develop both evidence-based guidelines and fair allocation of National Health Service (NHS) resources.

Table 1.1 Examples of harmful practices once strongly supported by 'expert opinion'

Approximate time period	Clinical practice accepted by experts of the day	Practice shown to be harmful in	Impact on clinical practice
From 500 bc	Blood letting (for just about any acute illness)	1820*	Blood letting ceased around 1910
1957	Thalidomide for 'morning sickness' in early pregnancy, which led to the birth of over 8000 severely malformed babies worldwide	1960	The teratogenic effects of this drug were so dramatic that thalidomide was rapidly withdrawn when the first case report appeared
From at least 1900	Bed rest for acute low back pain	1986	Many doctors still advise people with back pain to 'rest up'
1960s	Benzodiazepines (e.g. diazepam) for mild anxiety and insomnia, initially marketed as 'non-addictive' but subsequently shown to cause severe dependence and withdrawal symptoms	1975	Benzodiazepine prescribing for these indications fell in the 1990s
1970s	Intravenous lignocaine in acute myocardial infarction, with a view to preventing arrhythmias, subsequently shown to have no overall benefit and in some cases to *cause* fatal arrhythmias	1974	Lignocaine continued to be given routinely until the mid 1980s
Late 1990s	Cox-2 inhibitors (a new class of non-steroidal anti-inflammatory drug), introduced for the treatment of arthritis, were later shown to increase the risk of heart attack and stroke	2004	Cox-2 inhibitors for pain were quickly withdrawn following some high-profile legal cases in the USA, though new uses for cancer treatment (where risks may be outweighed by benefits) are now being explored

* Interestingly, blood letting was probably the first practice for which a randomised controlled trial was suggested. The physician Van Helmont issued this challenge to his colleagues as early as 1662: '*Let us take 200 or 500 poor people that have fevers. Let us cast lots, that one half of them may fall to my share, and the others to yours. I will cure them without blood-letting, but you do as you know – and we shall see how many funerals both of us shall have*'.[12] I am grateful to Matthias Egger for drawing my attention to this example.

There is one more reason why some people find the term ‘evidence-based medicine’ unpalatable. This chapter has argued that EBM is about coping with change, not about knowing all the answers before you start. In other words, it is not so much about what you have read in the past, but about how you go about identifying and meeting your ongoing learning needs and applying your knowledge appropriately and consistently in new clinical situations. Doctors who were brought up in the old school style of never admitting ignorance may find it hard to accept that a major element of scientific uncertainty exists in practically every clinical encounter, though in most cases, the clinician fails to identify the uncertainty or to articulate it in terms of an answerable question (see next section). If you are interested in the research evidence on doctors’ [lack of] questioning behaviour, see an excellent review by Deborah Swinglehurst.[13]

The fact that none of us – not even the cleverest or most experienced – can answer all the questions that arise in the average clinical encounter means that the ‘expert’ is more fallible than he or she was traditionally cracked up to be. An evidence-based approach to ward rounds may turn the traditional medical hierarchy on its head when the staff nurse or junior doctor produces new evidence that challenges what the consultant taught everyone last week. For some senior clinicians, learning the skills of critical appraisal is the least of their problems in adjusting to an evidence-based teaching style.

1.3 Before you start: formulate the problem

When I ask my medical students to write me an essay about high blood pressure, they often produce long, scholarly and essentially correct statements on what high blood pressure is, what causes it and what the treatment options are. On the day they hand their essays in, most of them know far more about high blood pressure than I do. They are certainly aware that high blood pressure is the single most common cause of stroke, and that detecting and treating everyone’s high blood pressure would cut the incidence of stroke by almost half. Most of them are aware that stroke, though devastating when it happens, is a fairly rare event, and that blood pressure tablets have side effects such as tiredness, dizziness, impotence and getting ‘caught short’ when a long way from the lavatory.

But when I ask my students a practical question such as ‘Mrs Jones has developed light-headedness on these blood pressure tablets and she wants to stop all medication; what would you advise her to do?’, they are foxed. They sympathise with Mrs Jones’ predicament, but they cannot distil from their pages of close-written text the one thing that Mrs Jones needs to know. As Richard Smith (paraphrasing TS Eliot) asked a few years ago in a *BMJ* editorial: ‘Where is the wisdom we have lost in knowledge, and the knowledge we have lost in information?’[14]

Experienced doctors (and nurses) might think they can answer Mrs Jones’ question from their own personal experience. As I argued in the previous

section, few of them would be right. And even if they were right on this occasion, they would still need an overall system for converting the rag-bag of information about a patient (an ill-defined set of symptoms, physical signs, test results and knowledge of what happened to this patient or a similar patient last time), the particular values and preferences (utilities) of the patient, and other things that could be relevant (a hunch, a half-remembered article, the opinion of a more experienced colleague or a paragraph discovered by chance while flicking through a textbook) into a succinct summary of what the problem is and what specific additional items of information we need to solve that problem.

Sackett and colleagues have helped us by dissecting the parts of a good clinical question:[15]

- First, define precisely *whom* the question is about (i.e. ask 'How would I describe a group of patients similar to this one?').
- Next, define *which* manoeuvre you are considering in this patient or population (e.g. a drug treatment), and, if necessary, a comparison manoeuvre (e.g. placebo or current standard therapy).
- Finally, define the desired (or undesired) *outcome* (e.g. reduced mortality, better quality of life, (QoL) overall cost savings to the health service and so on).

The second step may not concern a drug treatment, surgical operation or other intervention. The manoeuvre could, for example, be the exposure to a putative carcinogen (something that might cause cancer) or the detection of a particular surrogate endpoint in a blood test or other investigation. (A surrogate endpoint, as Section 6.3 explains, is something that predicts, or is said to predict, the later development or progression of disease. In reality, there are very few tests which reliably act as crystal balls for patients' medical future. The statement 'The doctor looked at the test results and told me I had six months to live' usually reflects either poor memory or irresponsible doctoring.) In both these cases, the 'outcome' would be the development of cancer (or some other disease) several years later. In most clinical problems with individual patients, however, the 'manoeuvre' consists of a specific intervention initiated by a health professional.

Thus, in Mrs Jones's case, we might ask, 'In a 68-year-old white woman with essential (i.e. common-or-garden) hypertension (high blood pressure), no coexisting illness and no significant past medical history, whose blood pressure is currently X/Y, do the benefits of continuing therapy with bendrofluazide (chiefly, reduced risk of stroke) outweigh the inconvenience?'. Note that in framing the specific question, we have already established that Mrs Jones has never had a heart attack, stroke or early warning signs such as transient paralysis or loss of vision. If she had, her risk of subsequent stroke would be much higher and we would, rightly, load the risk–benefit equation to reflect this.

In order to answer the question we have posed, we must determine not just the risk of stroke in untreated hypertension, but also the likely reduction in that risk which we can expect with drug treatment. This is, in fact, a rephrasing of a more general question (do the benefits of treatment in this case outweigh the risks?) which we should have asked before we prescribed bendrofluazide to

Mrs Jones in the first place, and which all doctors should, of course, ask themselves every time they reach for their prescription pad.

Remember that Mrs Jones' alternative to staying on this particular drug is not necessarily to take no drugs at all; there may be other drugs with equivalent efficacy but less disabling side effects (as Chapter 6 argues, too many clinical trials of new drugs compare the product with placebo rather than with the best available alternative), or non-medical treatments such as exercise, salt restriction, homeopathy or acupuncture. Not all of these approaches would help Mrs Jones or be acceptable to her, but it would be quite appropriate to seek evidence as to *whether* they might help her.

We will probably find answers to some of these questions in the medical literature, and Chapter 2 describes how to search for relevant papers once you have formulated the problem. But before you start, give one last thought to your patient with high blood pressure. In order to determine her personal priorities (how does she value a 10% reduction in her risk of stroke in 5 years' time compared to the inability to go shopping unaccompanied today?), you will need to approach Mrs Jones, not a blood pressure specialist or the Medline database.

Some writers on EBM are enthusiastic about using a decision-tree approach to incorporate the patient's perspective into an evidence-based treatment choice. In practice, this often proves impossible, because patients' experiences are complex stories that refuse to be reduced to a tree of yes/no decisions. Perhaps the most powerful criticism of EBM is that, if misapplied, it dismisses the patient's own perspective on their illness in favour of an average effect on a population sample or a column of QALYs (see Chapter 11) calculated by a medical statistician.

When preparing this edition of this introductory book, I found it difficult to resist the temptation to stray into more advanced (and interesting) topics, but these are properly a subject for a different textbook. Readers who feel ready to extend their knowledge of EBM and its application might like to explore new developments such as predicting diagnosis based on clinical observations,[16] incorporating the patient's perspective in clinical decision-making,[17,18] systematically considering the context in which the evidence is to be applied,[19] and combining EBM with the study of collective judgements in 'evidence-based policymaking'.[20]

EXERCISE 1

1 Go back to the fourth paragraph in this chapter, where examples of clinical questions are given. Decide whether each of these is a properly focused question in terms of:

a) the patient or problem;

b) the manoeuvre (intervention, prognostic marker, exposure);

c) the comparison manoeuvre, if appropriate;

d) the clinical outcome.

2 Now try the following:

a) A 5-year-old child has been on high-dose topical steroids for severe eczema since the age of 20 months. The mother believes that the steroids are stunting the child's growth, and wishes to change to

homeopathic treatment. What information does the dermatologist need to decide (a) whether she is right about the topical steroids and (b) whether homeopathic treatment will help this child?

b) A woman who is 9 weeks pregnant calls out her GP because of abdominal pain and bleeding. A previous ultrasound scan showed that the pregnancy was not ectopic. The GP decides that she might be having a miscarriage and tells her she must go into hospital for a scan and, possibly, an operation to clear out the womb. The woman would prefer to be treated at home. What information do they both need in order to establish whether hospital admission is medically necessary?

c) In the UK, most parents take their babies at the ages of 6 weeks, 8 months, 18 months and 3 years for developmental checks, where a doctor listens for heart murmurs, feels the abdomen and checks that the testicles are present, and a nurse shakes a rattle and counts how many bricks the infant can build into a tower. Ignoring the social aspects of 'well-baby clinics', what information would you need to decide whether the service is a good use of health resources?

References

1 Sackett DL, Rosenberg WC, Gray JAM. Evidence based medicine: what it is and what it isn't. *BMJ* 1996;**312**:71–72.

2 Sackett D, Haynes B. On the need for evidence-based medicine. *Evid Based Med* 1995;**1**:4–5.

3 Greenhalgh T. 'Is my practice evidence-based?' *BMJ* 1996;**313**(7063):957–958.

4 Cohen AM, Stavri PZ, Hersh WR. A categorization and analysis of the criticisms of Evidence-Based Medicine. *Int J Med Inform* 2004;**73**(1):35–43.

5 Dubinsky M, Ferguson JH. Analysis of the National Institutes of Health Medicare Coverage Assessment. *Int J Technol Assess Health Care* 1990;**6**:480–488.

6 Ellis J, Mulligan I, Rowe J, Sackett DL. Inpatient general medicine is evidence-based. *Lancet* 1995;**346**:407–410.

7 Macnaughton J. Anecdote in clinical practice. In: Greenhalgh T, Hurwitz B, editors. *Narrative based medicine: dialogue and discourse in clinical practice*. London: BMJ Publications; 1998.

8 Greenhalgh T, Hurwitz B. Narrative based medicine: why study narrative? *BMJ* 1999;**318**(7175):48–50.

9 Greenhalgh T. Intuition and evidence – uneasy bedfellows? *Br J Gen Pract* 2002;**52**(478):395–400.

10 Greenhalgh T. Narrative based medicine: narrative based medicine in an evidence based world. *BMJ* 1999;**318**(7179):323–325.

11 Mulrow C. Rationale for systematic reviews. *BMJ* 1995;**309**:597–599.

12 van Helmont JA. *Oriatrike, or physick refined: the common errors therein refuted and the whole art reformed and rectified*. London: Lodowick-Loyd; 1662.

13 Swinglehurst DA. Information needs of United Kingdom primary care clinicians. *Health Info Libr J* 2005;**22**:196–204.

14 Smith R. Where is the wisdom. . .? *BMJ* 1991;**303**:798–799.

15 Sackett DL, Richardson WS, Rosenberg WMC, Haynes RB. *Evidence-based medicine: how to practice and teach EBM* (2nd edition). London: Churchill-Livingstone; 2000.

16 Falk G, Fahey T. Clinical prediction rules. *BMJ* 2009;**339**(aug07_2):b2899.

17 Boote J, Telford R, Cooper C. Consumer involvement in health research: a review and research agenda. *Health Policy* 2002;**61**(2):213–236.

18 Entwistle VA, O'Donnell M. Research funding organisations and consumer involvement. *J Health Serv Res Policy* 2003;**8**(3):129–131.

19 Green L, Glasgow R. Evaluating the relevance, generalization, and applicability of research: issues in external validation and translation methodology. *Eval Health Prof* 2006;**29**(1):126–153.

20 Greenhalgh T, Russell J. Evidence-based policymaking: a critique. *Perspect Biol Med* 2009;**52**(2):304–318.

Chapter 2 Searching the literature

Co-authored with Jeanette Buckingham

Health professionals are under continuous pressure to work with information, to make use of it themselves for their own professional development and to help their patients find and use it and so participate in decision-making for their own care. Evidence-based health care, which all clinicians are encouraged to practice, requires the ability to navigate the research literature. Evidence is accumulating faster than ever before, and staying current is essential for quality patient care.

Studies and reviews of studies of physicians' information-seeking behaviour confirm that textbooks and personal contacts continue to be the most favoured sources for clinical information, followed by journal articles.[1–3]. Use of the Internet as an information resource has increased dramatically in recent years, especially via PubMed/Medline, but the sophistication of searching and the efficiency in finding answers has not grown apace.[4] While the need of health care professionals for information of the best quality has never been greater, barriers abound: lack of time, lack of facilities, lack of searching skills, lack of motivation and (perhaps worst of all) information overload.[5]

The medical literature is no less a jungle than it was when the first edition of this book was published. The volume and complexity of published literature has grown: Medline alone is pushing towards 20 million references. While Medline is the flagship database for journal articles in the health sciences, it is a very conservative resource, slow to pick up new journals or journals published outside the United States, so there are many thousands of high-quality papers that may be available via other databases but are not included in Medline's 20 million. The proliferation of databases (Box 2.1) makes the information jungle that much more confusing, especially since each database covers its own range of journals and each has its own particular search protocols. How is a person unschooled in the vagaries of information science to cope?

Box 2.1 Examples of 'raw' databases and indexes

Medline

Pre-Medline (unindexed articles, which may or may not be destined for inclusion in Medline)

EMBASE

CINAHL

Web of Science (including Science Citation Index and Social Sciences Citation Index)

PsychInfo

Global Health

Scopus

Google Scholar

There is hope: in the past decade the information 'jungle' has been tamed by means of information highways and high-speed transit systems. Knowing how to access these navigational wonders will make it easier and quicker to practise evidence-based health care. The purpose of this chapter is not to teach you to become an expert searcher, but rather to help you recognise the kinds of resources that are available, choose intelligently among them and put them to work directly.

2.1 What are you looking for?

A searcher may approach medical (and, more broadly, health science) literature for three broad purposes:

- Informally, almost recreationally, browsing to keep current and to satisfy our intrinsic curiosity;
- Focused, looking for answers, perhaps related to questions that have occurred in clinic or that arise from individual patients and their questions;
- Surveying the existing literature, perhaps before embarking on a research project.

Each approach involves searching in a very different way.

Browsing has an element of serendipity about it. We pick up our favourite journal – we may still have a personal paper subscription (a luxury not often found in health libraries in recent years) – and follow where our fancy takes us. If our fancy is informed with a few tools to help us discriminate the quality of papers we have found, so much the better. However, we can also make use of some new tools to help us with our browsing. We can browse electronic journals just as easily as paper journals; we can use alerting services to let us know when a new issue has been published and even tell us if articles matching our interest profile are in that issue. We can have RSS feeds of articles from particular journals or on particular topics sent to our email addresses or our i-Phones or personal blogs, and we can participate in Twitter related to newly published papers. Almost every journal has links from its home page allowing at least one of these social networking services. These technologies are changing continuously. Those of us who have been faced with deluges of new off-prints, photocopies and journal issues we have been meaning to read will be happy to learn that we can create the same chaos electronically. That is what browsing serendipitously is all about, and it is a joy we should never lose, in whatever medium our literature may be published.

Box 2.2 Databases of pre-appraised articles

Cochrane Controlled Clinical Trials Register

Health Technolgoy Assessment

NHS Economic Evaluation Database

Evidence-based digests – e.g. ACP Journal Club, Evidence Based Cardiology, Evidence Based Eye Care, Evidence Based Medicine, Evidence Based Mental Health, Evidence Based Nursing

Looking for answers implies a much more focused approach, a search for an answer we can trust to apply directly to the care of a patient. When we find that

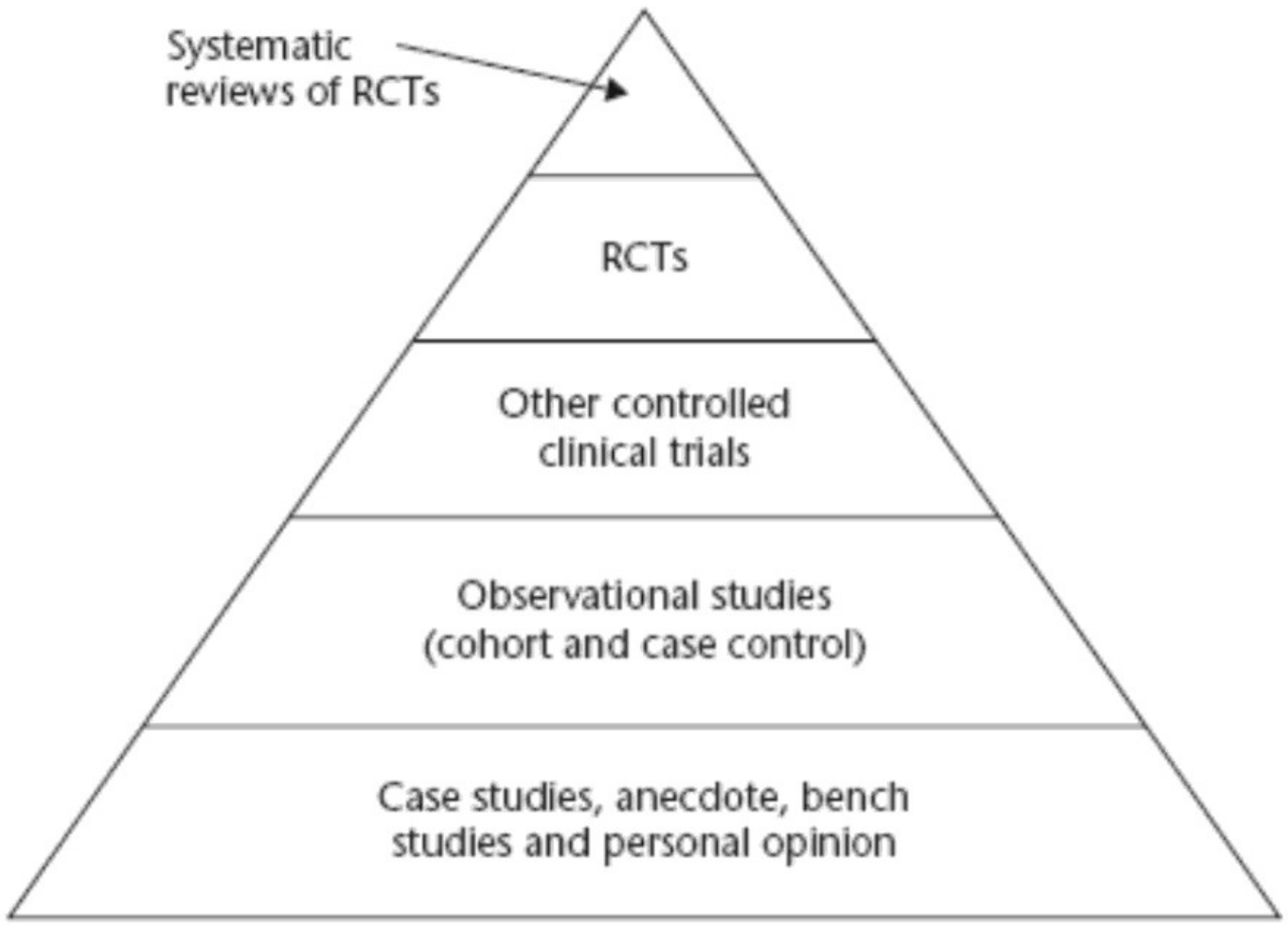
trustworthy information, it is OK to stop looking – we don't need to beat the bush for absolutely every study that may have addressed this topic. This kind of query is increasingly well served by new synthesised information sources whose goal is to support evidence-based care and the transfer of research findings into practice, and by filters built into some databases and compilations of pre-appraised articles (Box 2.2). These are discussed further below.

Surveying the literature – preparing a detailed, broad-based thoughtful literature review – involves an entirely different process. The purpose here is less to influence patient care directly than to identify the existing body of research that has addressed a problem and clarify the gaps in knowledge that require further research. This type of literature search typically provides the basis for research grant proposals, writing reviews and identifying new research directions ('scoping'). For this kind of searching, a strong knowledge of information resources and skill in searching them are fundamental. A simple PubMed search will not suffice. Multiple relevant databases need to be searched systematically, and citation chaining needs to be employed to assure that no stone has been left unturned. If this is your goal, you *must* consult with an information professional (health librarian, clinical informationist, etc.). Indeed, many grant-giving bodies and publishers now require the involvement of these professionals.

2.2 Levels upon levels of evidence

The term 'level of evidence' refers to what degree that information can be trusted, based on study design. Traditionally – if a decade or so of use can constitute a tradition – levels of evidence are represented as a pyramid, with systematic reviews positioned grandly at the top, followed by well-designed randomised controlled trials (RCTs), then observational studies such as cohort studies or case-control studies, with case studies, bench studies and 'expert opinion' somewhere near the bottom (Figure 2.1). A more complex representation of the hierarchy of evidence geared to the domain of the question (therapy/prevention, diagnosis, harm, prognosis) on the Centre of Evidence-based Medicine's website, http://www.cebm.net/index.aspx?o=1025.

Figure 2.1 A simple hierarchy of evidence for assessing the quality of trial design in therapy studies.



However, the emergence of more sophisticated types of resources has produced another pyramid, with computerised decision support systems at the top. These systems link relevant and important clinical research to patient records. Second in the scale of things would be evidence-based practice guidelines, followed by systematic review synopses with critical appraisal (such as that found in evidence-based digests or DARE, the Database of Abstracts of Reviews of Effects). In this pyramid, systematic reviews would lie beneath these, then the evidence-based digests themselves and finally the primary research – the original articles on which the entire pyramid is based.[6]

Whether we think in terms of the first (traditional) evidence pyramid or the second (more contemporary) one, the message is clear: all evidence, all information, is not necessarily equivalent. We need to keep a sharp eye out for the believability of whatever information we find, wherever we find it.

2.3 Synthesised sources: systems, summaries and syntheses

Information resources synthesised from primary studies (Box 2.3) constitute a very high level of evidence indeed. These resources exist to help translate research into practice and inform physician and patient decision-making. They are all relatively new (at least, compared to traditional primary studies, which have been with us for centuries), but their use is expected to grow considerably as they become better known.

Systematic reviews are perhaps the oldest and best known of the synthesised sources, having started in the 1980s under the inspiration of Archie Cochrane, who bemoaned the multiplicity of individual clinical trials whose information failed to translate into practice. The original efforts to search broadly for clinical trials on a topic and pool their results statistically grew into the Cochrane Library in the mid-1990s; Cochrane Reviews became the gold standard for systematic reviews and

the Cochrane Collaboration the premier force for developing and improving review methodology.

Box 2.3 Databases of synthesised evidence

American College of Physicians PIER

BMJ Point-of-Care

Clinical Evidence

Cochrane Database of Systematic Reviews (CDSR)

Database of Abstracts of Reviews of Effectiveness (DARE)

Dynamed

There are many advantages to systematic reviews and a few cautions. On the plus side, systematic reviews are easy to interpret. The systematic selection and appraisal of the primary studies according to an approved protocol means that bias is minimised. Smaller studies, which may be the norm in many topic areas, may show a trend towards positive impact but lack statistical significance. But as Chapter 9 shows, when data from several small studies are pooled into a meta-analysis, the combined data may produce a statistically significant finding. Systematic reviews can help resolve contradictory findings among different studies on the same question. If the systematic review has been properly conducted, the results are likely to be robust and generalisable. On the negative side, systematic reviews can replicate and magnify flaws in the original studies (e.g. if all the primary studies considered a drug at sub-therapeutic dose, the overall – misleading – conclusion may be that the drug has 'no effect'). Cochrane Reviews can be a daunting read, but here's a tip. The bulk of a Cochrane Review consists of methodological discussion: the gist of it can be gleaned by jumping to the 'Plain Language Summary', directly following the abstract. Alternatively, you can gain a quick and accurate summary by looking at the figures – especially something called a 'forest plot', which graphically displays the results of each of the primary studies along with the combined result.

Cochrane Reviews are only published electronically, but other systematic reviews appear throughout the clinical literature. They are most easily accessed via the Cochrane Library, which publishes Cochrane Reviews, DARE (listed in Cochrane Library as 'Other reviews'), and a database of Health Technology Assessments (HTAs). DARE provides not only a bibliography of systematic reviews, but also a critical appraisal of most of the reviews included, making this a pre-appraised source for systematic reviews. HTAs are essentially systematic reviews but range further to consider economic and policy implications of drugs, technologies and health systems. All may be searched relatively simply and simultaneously via the Cochrane Library.

In the past, Cochrane Reviews focused mainly on questions of therapy (see Chapter 6) or prevention, but since 2008, considerable effort has gone into producing systematic reviews of diagnostic tests (see Chapter 8).

Point of care resources are rather like electronic textbooks or detailed clinical handbooks, but explicitly evidence-based and continuously updated. A review of studies of the information-seeking behaviours of physicians[1] indicated that, in most studies, textbooks were the preferred source of information, followed generally by 'humans' (meaning colleagues and faculty). Point of care resources could well be

line'.

You can think of all these sources as small databases of selected studies, which may be searched by keyword. Other selected journal article services, such as Evidence Updates, provide abstracts plus an indication of level of interest each article might hold for particular disciplines.

DARE was mentioned above as a pre-appraised source for systematic reviews other than Cochrane Reviews, in that it provides an augmented abstract and a brief critical appraisal for most systematic reviews in its database.

Another source that is considered 'pre-appraised' is the *Central Register of Controlled Trials*, also part of the Cochrane Library (though this register does not include a critical appraisal on each study). 'Central' refers to the database of all studies that have been included in Cochrane Reviews, as well as new studies on similar topics, maintained by the various Cochrane Review Groups. DARE, Central, the Cochrane Database of Systematic Reviews, the HTA database and the NHS Economic Evaluation Database may all be searched simultaneously in the Cochrane Library.

2.5 Specialised resources

Before leaving the newly hewn paths through the health information jungle, do consider specialised information sources, organised to assist consultants in these fields, but potentially very useful for generalists and primary care clinicians as well. Most professional associations maintain excellent websites with practice guidelines, journal links and other useful information resources; most require membership in the association to access educational and practice materials. Three notable examples that are available for a fee are GIDEON, Psychiatry Online and CardioSource.

- GIDEON (Global Infectious Diseases and Epidemiology Network, http://www.gideononline.com/) is an evidence-based programme that assists with diagnosis and treatment of communicable diseases. In addition, GIDEON tracks incidence and prevalence of diseases worldwide and includes the spectrum covered by antibiotic agents. The opening screen asks detailed questions about symptoms and time and place of exposure, then suggests possible diagnoses, with links to appropriate treatments, microbiology and global epidemiological information. This resource is of special interest in a time when global travel is common and concern about large-scale epidemics is high.
- Psychiatry Online (http://www.psychiatryonline.com/) is a compendium of core textbooks, psychiatry journals and practice guidelines of the American Psychiatric Association, produced by the American Psychiatric Press.
- CardioSource (http://www.cardiosource.com) is produced by the American College of Cardiology. It includes guidelines, journal and textbook links, 'clinical collections' of articles and educational materials on topics such as cholesterol management and atrial fibrillation, and an excellent clinical trials registry for all trials relating to cardiovascular disease, whether ongoing or completed.

2.6 Primary studies – tackling the jungle

Whether through habit or lack of familiarity with synthesised, summarised or pre-appraised sources, most health practitioners still prefer a basic search of Medline/Pubmed to answer their clinical information needs.[4] Assessing the primary literature for yourself, without thumbnail critical appraisals or incorporation into larger disease management recommendations or guidelines, can be rewarding and the more you do it the better you will get. What help is there for those who prefer to search directly for primary sources?

Primary sources can be found in a variety of ways. One way of finding them is to follow the links in the synthesised and pre-appraised sources described in the previous sections. You can also of course browse or hand search the journals themselves, or ask arrange to receive RSS feeds, table-of-contents services or more focused topical information services by email. But most commonly, you will want to search bibliographic databases such as PubMed/Medline, EMBASE, PASCAL, Cochrane Library, CINAHL (Cumulated Index of Nursing and Allied Health Literature), Biosis Previews, Web of Science, Scopus, or Google or Google Scholar.

PubMed is the most frequently accessed Internet resource for most physicians and health professionals worldwide, possibly because it is free. Most people opt for the basic PubMed search, using 2 or 3 search text words at best[2,9] and characteristically turning up too many references, of which they look at the first couple of screens. Possibly not the most efficient way to search, but it seems to suffice for many. Interestingly, when a couple more search terms are added, the efficiency of searches improves substantially.[9]

Simple tools that are part of the Medline search engine can be used to help focus a search and produce better results for a basic search (Box 2.5). Unfortunately, these simple expedients are often not used by health practitioners. One such tool is the ‘limit’ function, allowing restrictions to such generic topics as gender, age group, or study design; to language; or to core clinical journals (Box 2.6). The advanced search function on PubMed incorporates these limits into a single search page.

‘Clinical queries’, an option provided in the left-hand panel of the basic PubMed screen or at the bottom of the advanced search screen, utilises elegantly formulated filters to extract study designs likely to provide best evidence to answer clinical question, specific to the domains of therapy/prevention, diagnosis, causation or prognosis (the filters were developed by Brian Haynes and his Hedges team; a bibliography of their validating studies is available at http://www.nlm.nih.gov.login.ezproxy.library.ualberta.ca/pubs/techbull/jf04/cq_info.html). Clinical queries superimpose on the search a filter based on optimum study designs for best evidence, depending on the domain of the question and the degree to which one wishes to focus the question; for example, if one were searching for a therapy study for hypercholesterolemia, the clinical query for therapy/narrow and specific would be rendered as ‘(hypercholesterolemia) AND (randomized controlled trial [Publication Type] OR (randomized[Title/Abstract] AND controlled[Title/Abstract] AND trial[Title/Abstract]))’. In this instance the search might need further limits or perhaps the addition of a second term, such as a specific drug, because the search produces over 2000 hits.

Box 2.4 Useful 'limit set' options

Core clinical journals

Nursing journals

Dental journals

Publication year

Review articles

Editorials

Abstracts

Age group

English language

Male/Female

Human

Box 2.5 Useful search field labels (OVID Medline)

Syntax	Meaning	Example
ab.	word in abstract	**epilepsy.ab.**
.au.	author	**smith-r.au.**
.jn.	journal	**lancet.jn.**
.me.	single word, wherever it may appear as a MeSH term	**ulcer.me.**
.sh.	exact MeSH heading	**lung neoplasms.sh.**
.ti.	word in title	**epilepsy.ti.**
.tw.	word in title or abstract	**epilepsy.tw.**
.ui.	unique identifier	**91574637.ui.**
.yr.	year of publication	**87.yr.**

Box 2.6 Useful subheadings (OVID Medline)

Syntax	Meaning	Example
/ae	adverse effects	**thalidomide/ae**
/ci	chemically induced	**headache/ci**
/co	complications	**measles/co**
/ct	contraindications [of drug]	**propranolol/ct**
/di	diagnosis	**glioma/di**
/dt	drug therapy	**depression/dt**
/ed	education	**asthma/ed**
/ep	epidemiology	**poliomyelitis/ep**
/et	etiology (aetiology)	**asthma/et**
/hi	history	**mastectomy/hi**
/nu	nursing	**cerebral palsy/nu**
/og	organisation/administration	**health service/og**
/pc	prevention and control	**influenza/pc**
/px	psychology	**diabetes/px**

/rh	rehabilitation	**hip fractures/rh**
/su	surgery	**hip fractures/su**
/th	therapy	**hypertension/th**
/tu	therapeutic use [of drug]	**aspirin/tu**

'Special Queries' are also available on the advanced search page of PubMed, but address a somewhat eclectic assortment of topics, including AIDS, Space Life Sciences, Health Disparities, Cancer, Bioethics and Complementary Medicine. However, the Hedges group has been at work developing more clinically relevant filters, which may appear in future PubMed iterations.[10]

Citation chaining (Box 2.7) provides another means of following a topic. Let's say that, following your interest in hypercholesterolemia, you wish to follow up the West Coast of Scotland Coronary Prevention Study. In your PubMed search above, you found a study in the New England Journal of Medicine in 2007 that provided some follow-up, but you wonder if there has been anything further. Web of Science, comprised of Science Citation Index, Social Sciences Citation Index and the Arts and Humanities Citation Index online, provides a cited reference search feature. Entering the author's name (in this case I. Ford) and the year of publication (2007), we can trace the specific article, and find that 55 other articles have cited it in their reference lists. Presuming that authors cite a paper because they are working on a similar problem, one can follow up these citing articles, and the articles citing them, to create a fascinating chain. One can go further, tracking articles that cite the same studies, again creating a rich mine of information. This is an especially powerful way to search for subjects that are interdisciplinary or difficult to find with established subject headings. Moreover, citation searching can indicate the relative importance of a study, based on the number of times it has been cited. Scopus is another, newer database that permits citation chaining, and indeed allows ranking of a particular author's published articles by the numbers of citations.

Google, a very broad-based web browser, has gained a large following, in some studies coming second only to PubMed/Medline.[11] For an obscure topic Google can be an excellent resource on which to fall back, covering PubMed as well as new open-access journals. Unfortunately, there are no quality filters like clinical queries, and you can't limit your set (e.g. by gender, age or language, but if you don't mind wading through tens of thousands of postings for most queries, Google may be the answer. Finally, to identify trials that have begun but are still in progress or not written up yet, try databases of ongoing research (Box 2.8).

Box 2.7 Citation searching (or chaining)

Web of Science, including Science Citation Index and Social Science Citation Index

PubMed 'related articles' function

Scopus

Box 2.8 Databases of ongoing research

UK National Research Register
https://portal.nihr.ac.uk/Pages/NRRArchive.aspx

Current Controlled Trials http://www.controlled-trials.com/

2.7 One-stop shopping: federated search engines

Perhaps the simplest and most efficient answer for most clinicians searching for information for patient care is a federated search engine such as TRIP, Turning Research into Practice, http://www.tripdatabase.com/ or SUMsearch, http://sumsearch.uthscsa.edu/. Both sources search multiple resources simultaneously and are free.

- *SUMsearch*, produced by the University of Texas, has an excellent search engine that facilitates a clear and focused search on a somewhat limited range of resources. One of the recommendations in the results from a SUMsearch query suggested a search of TRIP.
- *TRIP* has a truly primitive search engine, but it searches synthesised sources (systematic reviews including Cochrane reviews), summarised sources (practice guidelines from North America, Europe, Australia/New Zealand and elsewhere, as well as electronic textbooks including the excellent peer-reviewed eMedicine), and pre-appraised sources (Evidence-based Medicine, Evidence-based Mental Health, etc.), as well as searching all clinical query domains in PubMed simultaneously. Moreover, searches can be limited by discipline, such as Paediatrics or Surgery, helping both to focus a search and eliminate clearly irrelevant results, and acknowledging the tendency of medical specialties to prefer the literature in their own journals. Given that most clinicians favour very simple searches, failing the availability of a broad evidence-based summarising resource such as ACP PIER or DynaMed, a TRIP search would probably produce the most satisfactory results from all types of information.

2.8 Asking for help and asking around

If a librarian fractured her wrist, she would have no hesitation in seeking out a physician. Similarly, a health care professional doesn't need to cope with the literature alone. Health librarians are readily available in universities, hospitals, government departments and agencies, and professional societies. They know the databases available, they know the complexities of searching, they know the literature (even complex government documents and obscure data sets), and they know just enough about the topic to have an idea of what you are looking for and levels of evidence that are likely to be found. When one librarian can't find an answer, there are colleagues with whom he or she can and will consult, locally, nationally and internationally.

Box 2.9 Human contact sources

Contact, Help, Advice and Information Network (CHAIN)

Academic mailing lists (see http://www.jiscmail.ac.uk) – e.g. evidence-based-health,

on the interest value of the hypothesis, the nature or potential impact of the results or the speculation in the discussion.

Conversely, bad science is bad science regardless of whether the study addressed an important clinical issue, whether the results are 'statistically significant' (see Section 5.5), whether things changed in the direction you would have liked them to, and whether, if true, the findings promise immeasurable benefits for patients or savings for the health service. Strictly speaking, *if you are going to trash a paper, you should do so before you even look at the results*.

It is much easier to pick holes in other people's work than to do a methodologically perfect piece of research oneself. When I teach critical appraisal, there is usually someone in the group who finds it profoundly discourteous to criticise research projects into which dedicated scientists have put the best years of their lives. On a more pragmatic note, there may be good practical reasons why the authors of the study have not performed a perfect study, and they know as well as you do that their work would have been more scientifically valid if this or that unforeseen difficulty had not arisen during the course of the study.

Most good scientific journals send papers out to a referee for comments on their scientific validity, originality and importance before deciding whether to print them. This process is known as *peer review*, and much has been written about it.[3] Common defects picked up by referees are listed in Box 3.1.

The assessment of methodological quality (critical appraisal) has been covered in detail in many textbooks on EBM,[4,5] and in the widely cited series led by Gordon Guyatt 'Users' Guides to the Medical Literature' (for the full list and links to the free full text of most of them, see the Center for Health Evidence, http://www.cche.net/usersguides/main.asp). The structured guides produced by these authors on how to read papers on therapy, diagnosis, screening, prognosis, causation, quality of care, economic analysis, systematic review, qualitative research and so on are regarded by many as the definitive checklists for critical appraisal. Appendix 1 lists some simpler checklists which I have derived from the Users' Guides and the other sources cited at the end of this chapter, together with some ideas of my own. If you are an experienced journal reader, these checklists will be largely self-explanatory. If, however, you still have difficulty getting started when looking at a medical paper, try asking the preliminary questions in the next section.

3.2 Three preliminary questions to get your bearings

Question One: *What was the research question – and why was the study needed?*

The introductory sentence of a research paper should state, in a nutshell, what the background to the research is. For example, 'Grommet insertion is a common procedure in children, and it has been suggested that not all

operations are clinically necessary'. This statement should be followed by a brief review of the published literature, for example 'Gupta and Brown's prospective survey of grommet insertions demonstrated that . . .'. It is irritatingly common for authors to forget to place their research in context, since the background to the problem is usually clear as daylight to them by the time they reach the writing-up stage.

Unless it has already been covered in the introduction, the methods section of the paper should state clearly the research question and/or the hypothesis that the authors have decided to test. For example: 'This study aimed to determine whether day case hernia surgery was safer and more acceptable to patients than the standard inpatient procedure'.

You may find that the research question has inadvertently been omitted, or, more commonly, that the information is buried somewhere in mid-paragraph. If the main research hypothesis is presented in the negative (which it usually is), such as 'The addition of metformin to maximal dose sulphonylurea therapy will not improve the control of Type 2 diabetes', it is known as a *null* hypothesis. The authors of a study rarely actually *believe* their null hypothesis when they embark on their research. Being human, they have usually set out to demonstrate a difference between the two arms of their study. But the way scientists do this is to say 'let's *assume* there's no difference; now let's try to disprove that theory'. If you adhere to the teachings of Karl Popper, this *hypotheticodeductive* approach (setting up falsifiable hypotheses which you then proceed to test) is the very essence of the scientific method.[6]

If you have not discovered what the authors' stated (or unstated) research question was by the time you are halfway through the methods section, you may find it in the first paragraph of the discussion. Remember, however, that not all research studies (even good ones) are set up to test a single definitive hypothesis. *Qualitative* research studies, which are as valid and as necessary as the more conventional quantitative studies, aim to look at particular issues in a broad, open-ended way in order to generate (or modify) hypotheses and prioritise areas to investigate. This type of research is discussed further in Chapter 12. Even quantitative research (which most of the rest of this book is about) is now seen as more than hypothesis-testing. As Section 5.5 argues, it is strictly preferable to talk about evaluating the *strength* of evidence around a particular issue than about proving or disproving hypotheses.

Question Two: *What was the research design?*

First, decide whether the paper describes a primary or secondary study. Primary studies report research first-hand, while secondary (or integrative) studies attempt to summarise and draw conclusions from primary studies. Primary studies (sometimes known as empirical studies) are the stuff of most published research in medical journals, and usually fall into one of four categories:

- *Laboratory experiments*, in which a manoeuvre is performed on an animal or a volunteer in artificial and controlled surroundings;