Clinical pharmacology

SYNOPSIS
Clinical pharmacology comprises all aspects of the scientific study of drugs in humans. Its objective is to optimise drug therapy and it is justified in so far as it is put to practical use.

Over the centuries humans have sought relief from discomfort in ‘remedies’ concocted from parts of plants, animals and other sources; numerous formulae attest to their numbers and complexity. Then a more critical view emerged, recognising the need for proper investigation of medications. In 1690, John Locke \(^1\) was moved to write ‘… we should be able to tell beforehand that rhubarb will purge, hemlock kill, and opium make a man sleep …’.

The early years of the 20th century saw the use of specific chemical substances to achieve particular biological effects, i.e. the exact science of drug action, which is pharmacology. Subsequently the discipline underwent a major expansion resulting from technology that allowed the understanding of molecular action and the capacity to exploit this. The potential consequences for drug therapy are enormous. All cellular mechanisms (normal and pathological), in their immense complexity are, in principle, identifiable. What seems almost an infinity of substances, transmitters, local hormones, cell growth factors, can be made, modified and tested to provide agonists, partial agonists, inverse agonists and antagonists. And the unravelling of the human genome opens the way for interference with disease processes in ways that were never thought possible.

Increasingly large numbers of substances will deserve to be investigated and used for altering physiology to the advantage of humans. And with all these developments and their potential for good, comes capacity for harm, whether inherent in the substances or as a result of human misapplication. Successful use of the power conferred (by biotechnology in particular) requires understanding of the growing evidence base of the true consequences of interference. The temporary celebrity of new drugs is not a new phenomenon. Jean Nicholas Corvisart (Emperor Napoleon’s favourite physician) reputedly expressed the issue in the dictum: ‘Here is a new remedy; take it fast, as long as it still works’.

Clinical Pharmacology Provides the Scientific Basis for:
- the general aspects of rational, safe and effective drug therapy
- drug therapy of individual diseases
- the safe introduction of new medicines.

The drug and information ‘explosion’ of the past six decades combined with medical need has called into being a new discipline, clinical pharmacology\(^2\). The discipline finds recognition as both a health-care and an academic specialty; indeed, no medical school can be considered complete without a department or sub-department of Clinical Pharmacology.

---

\(^1\) Locke J 1690 An essay concerning human understanding. Clarendon Press, Oxford, Book iv, Chapter iii, p 556. The English philosopher John Locke (1632–1704) argued that all human knowledge came only from experience and sensations.

\(^2\) The term was first used by Paul Martini (1889–1964). He addressed issues that are now integral parts of part of clinical trials, including the use of placebo, control groups, sample size, relationship between dose and response, probability of efficacy. His monograph, ‘Methodology of therapeutic investigation’ (Springer, Berlin, 1932), was published in German and went largely unnoticed by English speakers. (Shelly J H, Baur M P 1999 Paul Martini: the first clinical pharmacologist? Lancet 353:1870–1873)
CLINICAL PHARMACOLOGY

A signal pioneer was Harry Gold3 (1899–1972) of Cornell University, USA, whose influential studies in the 1930s showed the qualities needed to be a clinical pharmacologist. In 1952, he wrote in a seminal article:

… a special kind of investigator is required, one whose training has equipped him not only with the principles and technics of laboratory pharmacology but also with knowledge of clinical medicine …

Clinical scientists of all kinds do not differ fundamentally from other biologists; they are set apart only to the extent that there are special difficulties and limitations, ethical and practical, in seeking knowledge from man.4

Willingness to learn the principles of pharmacology, and how to apply them in individual circumstances of infinite variety is vital to success without harm: to maximise benefit and minimise risk. All of these issues are the concern of clinical pharmacology and are the subject of this book.

More detailed aspects comprise:

1. Pharmacology
   ■ Pharmacodynamics: how drugs, alone and in combination, affect the body (young, old, well, sick)
   ■ Pharmacokinetics: absorption, distribution, metabolism, excretion or, how the body, well or sick, affects drugs

2. Therapeutic evaluation
   ■ Whether a drug is of value
   ■ How it may best be used
   ■ Formal therapeutic trials
   ■ Surveillance studies for both efficacy and safety (adverse effects) – pharmacoepidemiology and pharmacovigilance

3. Control
   ■ Rational prescribing and formularies
   ■ Official regulation of medicines
   ■ Social aspects of the use and misuse of medicines
   ■ Pharmacoeconomics.

Clinical pharmacology finds expression in concert with other clinical specialties. Therapeutic success with drugs is becoming more and more dependent on the user having at least an outline understanding of both pharmacodynamics and pharmacokinetics. This outline is quite simple and easy to acquire. However humane and caring doctors may be, they cannot dispense with scientific skill. Knowledge of clinical pharmacology underpins decisions in therapeutics, which is concerned with the prevention, suppression or cure of disease and, from the point of view of society, is the most vital aspect of medicine.

Pharmacology is the same science whether it investigates animals or humans. The need for it grows rapidly as not only scientists, but now the whole community, can see its promise of release from distress and premature death over yet wider fields. The concomitant dangers of drugs (fetal deformities, adverse reactions, dependence) only add to the need for the systematic and ethical application of science to drug development, evaluation, and use, i.e. clinical pharmacology.

---

3 Gold H 1952 The proper study of mankind is man. American Journal of Medicine 12:619. The title is taken from ‘An essay on man’ by Alexander Pope (English poet, 1688–1744) which begins with the lines: ‘Know then thyself, presume no God to scan,/The proper study of mankind is man’. Indeed, the whole passage is worth accessing, for it reads as if it were God to scan,


---

GUIDE TO FURTHER READING

Reidenberg M M 1999 Clinical pharmacology: the scientific basis of therapeutics. Clinical Pharmacology and Therapeutics 66:2–8
The use of drugs to increase human happiness by elimination or suppression of diseases and symptoms and to improve the quality of life in other ways is a serious matter. Overall, the major benefits of modern drugs are on quality of life (measured with difficulty), and exceed those on quantity of life (measured with ease). This chapter comprises a series of essays on what we think are important topics.

Medicines are part of our way of life from birth, when we enter the world with the aid of drugs, to death where drugs assist (most of) us to depart with minimal distress and perhaps even with a remnant of dignity. In between these events, we use drugs to cure, suppress and prevent disease, and to regulate our fertility. We tend to take such usages for granted. But the average person in the USA can expect to have about 12 years of bad health in an average lifespan. And medicines play a major role in this. At any time, 40–50% of adults [UK] are taking a prescribed medicine.

Readers of this book will become aware that the medicines now available to prescribers emanate from a long process of evaluation (Chapters 3–6). The

A drug is a single chemical substance that forms the active ingredient of a medicine (a substance or mixture of substances used in restoring or preserving health). A medicine may contain many other substances to deliver the drug in a stable form, acceptable and convenient to the patient. The terms are used more or less interchangeably in this book. To use the word 'drug' intending only a harmful, dangerous or addictive substance is to abuse a respectable and useful word.

Consider the worldwide total of suffering relieved and prevented each day by anaesthetics (local and general) and by analgesics, not forgetting dentistry which, because of these drugs, no longer strikes terror into even the most stoical as it has done for centuries. 3

A World Health Organization Scientific Group has defined a drug as 'any substance or product that is used or, intended to be used, to modify or explore physiological systems or pathological states for the benefit of the recipient'. WHO 1966 Technical Report Series no. 341:7. A less restrictive definition is 'a substance that changes 'a biological system by interacting with it'.

1A World Health Organization Scientific Group has defined a drug as 'any substance or product that is used or, intended to be used, to modify or explore physiological systems or pathological states for the benefit of the recipient'. WHO 1966 Technical Report Series no. 341:7. A less restrictive definition is 'a substance that changes 'a biological system by interacting with it'.

2Consider the worldwide total of suffering relieved and prevented each day by anaesthetics (local and general) and by analgesics, not forgetting dentistry which, because of these drugs, no longer strikes terror into even the most stoical as it has done for centuries.

3Quoted in: USA Public Health Service 1995.

4George C F 1994 What do patients need to know about prescribed drugs? Prescribers’ Journal 34:7. A moment’s reflection will bring home to us that this is an astounding statistic, which goes a long way to account for the aggressive promotional activities of the highly competitive international pharmaceutical industry; the markets for medicines are colossal.

The desire to take medicines is perhaps the greatest feature that distinguishes humans from animals (Sir William Osler, 1849–1919).
science of pharmacology provides the information base for the creation of new drugs and the understanding of how they act, how unwanted and toxic effects occur, and how they are best used. Increasingly, the disciplines of pharmacogenetics and pharmacogenomics will provide the means to match individual patients with drugs that give them best effect for least harm (Chapters 7–10). The general account of drugs (Chapters 11–38) and their use in a spectrum of conditions indicates the vast resource open to modern physicians. A picture emerges of progressive appraisal (punctuated by learning from mistakes) within regulated systems to produce a large number of medicines that meet set standards of safety and efficacy. The scenario is comparatively recent.

From the earliest times, alleviating effects of disease and trauma was a major concern of human beings. Records of the ancient civilisations of Mesopotamia (now Iraq), India, China, Mexico and Egypt, from about 3000 BC, describe practices and belief systems of therapy, a reliance on diet and use of herbs (the Mexicans knew of 1200 medicinal plants) figured prominently.

The Greeks (approximately 500 BC to AD 500) replaced the supernatural with thinking that was rational, scientific and naturalistic. The core concept of the Hippocratic corpus (collected contributions of many writers but attributed to Hippocrates) was that health was an equilibrium, and disease an disequilibrium, of the four constituent fluids or ‘humours’ of the body. They comprised yellow bile and phlegm (exuded in illness), blood (associated with life) and black bile (a later addition, possibly altered blood in vomit and excreta). These humours were in symmetry with four fundamental qualities of nature – hot, wet, dry and cold – and gave rise to the system of allopathy, i.e. treating the first condition (the disease) by producing a second condition that was antagonistic to it. An illness involving yellow bile, regarded as ‘hot’ and dry, thus required a ‘cold’ and ‘wet’ medication (cf. homoeopathy; see p. 000). Disease as a disequilibrium of humours was correctable by evacuation techniques to re-establish the balance, and hence came venesection, cathartics, sweating and emetics. The remarkable Galen of Pergamum (AD 130–201) propagated Hippocratic principles so effectively that they dominated medical thinking to the Middle Ages and beyond. In effect, medicine through this time was stagnant. Life was ‘nasty, brutish and short’, and medical care did little to help.

The unravelling of the structure and later the function of the human body was part of the scientific resurgence of the Renaissance. Amongst many discoveries, William Harvey (1578–1657) explained the circulation of the blood, and Antoine Lavoisier (1743–1794) the crucial nature of oxygen. The human body, hitherto a mystery, appeared more like a machine – that could experience faults. But faults were interpreted in various ways. William Cullen of Edinburgh (1712–1790) evolved a system within which a ‘nervous force’ was the phenomenon underlying life and disease. His pupil, John Brown (1735–1778), went further and revived an ancient belief that every disease resulted from sthenia (over-stimulation) or asthenia (failure to respond to stimulation).

It was only in the 19th century that medicine freed itself from a muddle of theories and systems. Microscopy revealed the cell as the basic construction unit of the body, vague theories of disease gave way to specific entities with recognisable pathology, most notably in the case of infection with microorganisms (‘germ theory’). The one major dimension of medicine that remained underdeveloped was therapeutics. An abundance of preparations in pharmacopoeias compared with a scarcity of genuinely effective therapies gave to a state of ‘therapeutic nihilism’, expressed trenchantly by Oliver Wendell Holmes (1809–1894):

*Throw out opium …; throw out a few specifics …; throw out wine, which is a food, and the vapours which produce the miracle of anaesthesia, and I firmly believe that if the whole materia medica, as now used, could be sunk to the bottom of the sea, it would be all the better for mankind, – and all the worse for the fishes.*

*Thomas Hobbes (1588–1679), political philosopher; in: Leviathan 1651.
The 20th century saw this position alter beyond recognition (see above).

Drug therapy involves a great deal more than matching the name of the drug to the name of a disease; it requires knowledge, judgement, skill and wisdom, but above all a sense of responsibility.

**TREATING PATIENTS WITH DRUGS**

A book can provide knowledge and contribute to the formation of judgement, but it can do little to impart skill and wisdom, which are the products of example of teachers and colleagues, of experience and of innate and acquired capacities. But:

It is evident that patients are not treated in a vacuum and that they respond to a variety of subtle forces around them in addition to the specific therapeutic agent.8

When a patient receives a drug, the response can be the resultant of numerous factors:

- The pharmacodynamic effect of the drug and interactions with any other drugs the patient may be taking
- The pharmacokinetics of the drug and its modification in the individual by genetic influences, disease, other drugs
- The act of medication, including the route of administration and the presence or absence of the doctor
- What the doctor has told the patient
- The patient’s past experience of doctors
- The patient’s estimate of what has been received and of what ought to happen as a result
- The social environment, e.g. whether it is supportive or dispiriting.

The relative importance of these factors varies according to circumstances. An unconscious patient with meningococcal meningitis does not have a personal relationship with the doctor, but patients, sleepless with anxiety because they cannot cope with their family responsibilities, may respond as much to the interaction of their own personalities with that of the doctor, as to anxiolytics.

The physician may consciously use all of the factors listed above in therapeutic practice. But it is still not enough that patients get better: it is essential to know why they do so. This is because potent drugs should be given only if their pharmacodynamic effects are needed; many adverse reactions have been shown to be due to drugs that are not needed, including some severe enough to cause hospital admission.

**Drugs can do good**

Medically, this good may sometimes seem trivial, as in the avoidance of a sleepless night in a noisy hotel or of social embarrassment from a profusely running nose due to seasonal pollen allergy (hay fever). Such benefits are not necessarily trivial to recipients, concerned to be at their best in important matters, whether of business, of pleasure or of passion, i.e. with quality of life.

Or the good may be literally life-saving, as in serious acute infections (pneumonia, septicaemia) or in the prevention of life-devastating disability from severe asthma, from epilepsy or from blindness due to glaucoma.

**Drugs can do harm**

This harm may be relatively trivial, as in hangover from a hypnotic or transient headache from glyceryl trinitrate used for angina.

The harm may be life-destroying, as in the rare sudden death following an injection of penicillin, rightly regarded as one of the safest of antibiotics, or the destruction of the quality of life that occasionally attends the use of drugs that are effective in rheumatoid arthritis (adrenocortical steroids, penicillamine) and Parkinson’s disease (levodopa).

There are risks in taking medicines, just as there are risks in food and transport. There are also risks in declining to take medicines when they are needed, just as there are risks in refusing food or transport when they are needed.

Efficacy and safety do not lie solely in the molecular structure of the drug. Doctors must choose which drugs to use and must apply them correctly in relation not only to their properties, but also to those of the patients and their disease. Then patients must use the prescribed medicine correctly (see Compliance/concordance below).

---

**TOPICS IN DRUG THERAPY**

**Uses of drugs/medicines**

Drugs are used in three principal ways:
- To cure disease: primary and auxiliary
- To suppress disease
- To prevent disease: (prophylaxis): primary and secondary.

**Cure** implies *primary* therapy, as in bacterial and parasitic infections, that eliminates the disease, and the drug is withdrawn; or *auxiliary* therapy, as with anaesthetics and with ergometrine and oxytocin in obstetrics.

**Suppression** of diseases or symptoms is used continuously or intermittently to avoid the effects of disease without attaining cure (as in hypertension, diabetes mellitus, epilepsy, asthma), or to control symptoms (such as pain and cough) whilst awaiting recovery from the causative disease.

**Prevention** (prophylaxis). In *primary prevention*, the person does not have the condition and avoids getting it. For malaria, vaccinations and contraception, the decision to treat healthy people is generally easy.

In *secondary prevention*, the patient has the disease and the objective is to reduce risk factors, so to retard progression or avoid repetition of an event, e.g. aspirin and lipid-lowering drugs in atherosclerosis and after myocardial infarction, antihypertensives to prevent recurrence of stroke.

Taking account of the above, a doctor might ask the following questions before treating a patient with drugs:

1. Should I interfere with the patient at all?
2. If so, what alteration in the patient’s condition do I hope to achieve?
3. Which drug is most likely to bring this about?
4. How can I administer the drug to attain the right concentration in the right place at the right time and for the right duration?
5. How will I know when I have achieved the objective?
6. What other effects might the drug produce, and are these harmful?
7. How will I decide to stop the drug?
8. Does the likelihood of benefit, and its importance, outweigh the likelihood of damage, and its importance, i.e. the benefit versus risk, or efficacy against safety?

**BENEFITS AND RISKS OF MEDICINES**

Modern technological medicine has been criticised, justly, for following the tradition of centuries by waiting for disease to occur and then trying to cure it rather than seeking to prevent it in the first place. Although many diseases are partly or wholly preventable by economic, social and behavioural means, these are too seldom adopted and are slow to take effect. In the meantime, people continue to fall sick, and to need and deserve treatment.

We all have eventually to die from something and, even after excessive practising of all the advice on how to live a healthy life, the likelihood that the mode of death for most of us will be free from pain, anxiety, cough, diarrhoea, paralysis (the list is endless) seems so small that it can be disregarded. Drugs already provide immeasurable solace in these situations, and the development of better drugs should be encouraged.

Doctors know the sick are thankful for drugs, just as even the most dedicated pedestrians and environmentalists struck down by a passing car are thankful for a motor ambulance to take them to hospital. The reader will find reference to the benefits of drugs in individual diseases throughout this book and further expansion is unnecessary here. But a general discussion of risk of adverse events is appropriate.

**Unavoidable Risks**

Consider, for the sake of argument, the features that a completely risk-free drug would exhibit:

- The physician would know exactly what action is required and use the drug correctly.
- The drug would deliver its desired action and nothing else, either by true biological selectivity or by selective targeted delivery.
- The drug would achieve exactly the right amount of action – neither too little, nor too much.

These criteria may be completely fulfilled, for example in a streptococcal infection sensitive to penicillin in patients whose genetic constitution does not render them liable to an allergic reaction to penicillin.

These criteria are partially fulfilled in insulin-deficient diabetes. But the natural modulation of insulin secretion in response to need (food, exercise) does not operate with injected insulin and even sophisticated technology cannot yet exactly mimic the normal physiological responses. The criteria are still further from realisation in, for example, some cancers and schizophrenia.
Some reasons why drugs fail to meet the criteria of being risk-free include:

- **Drugs may be insufficiently selective.** As the concentration rises, a drug that acts at only one site at low concentrations begins to affect other target sites (receptors, enzymes) and recruit new (unwanted) actions; or a disease process (cancer) is so close to normal cellular mechanisms that perfectly selective cell kill is impossible.

- **Drugs may be highly selective for one pathway but the mechanism affected has widespread functions and interference with it cannot be limited to one site only,** e.g. atenolol on the \( \beta \)-adrenoceptor, aspirin on cyclo-oxygenase.

- **Prolonged modification of cellular mechanisms can lead to permanent change in structure and function,** e.g. carcinogenicity.

- **Insufficient knowledge of disease processes** (some cardiac arrhythmias) and of drug action can lead to interventions that, although undertaken with the best intentions, are harmful.

- **Patients are genetically heterogeneous to an high degree** and may have unpredicted responses to drugs.

- **Dosage adjustment according to need is often unavoidably imprecise,** e.g. in depression.

- **Prescribing 'without due care and attention'**.9

**Reduction of risk**

Strategies that can limit risk include those directed at achieving:

- **Better knowledge of disease (research)** – as much as 40% of useful medical advances derive from basic research that was not funded towards a specific practical outcome

- **Site-specific effect** – by molecular manipulation

- **Site-specific delivery** – drug targeting:  
  - by topical (local) application  
  - by target-selective carriers.

- **Informed, careful and responsible prescribing.**

**Two broad categories of risk**

*First are those that we accept by deliberate choice.* We do so even if we do not exactly know their magnitude, or we know but wish they were smaller, or, especially where the likelihood of harm is sufficiently remote though the consequences may be grave, we do not even think about the matter. Such risks include transport and sports, both of which are inescapably subject to potent physical laws such as gravity and momentum, and surgery to rectify disorders that we could tolerate or treat in other ways, e.g. much cosmetic surgery.

*Second are those risks that cannot be significantly altered by individual action.* We experience risks imposed by food additives (preservatives, colouring), air pollution and some environmental radioactivity. But there are also risks imposed by nature, such as skin cancer due to excess ultraviolet radiation in sunny climes, as well as some radioactivity.

It seems an obvious course to avoid unnecessary risks, but there is disagreement on what risks are truly unnecessary and, on looking closely at the matter, it is plain that many people habitually take risks in their daily and recreational life that it would be a misuse of words to describe as necessary. Furthermore, some risks, although known to exist, are, in practice, ignored other than by conforming to ordinary prudent conduct. These risks are negligible in the sense that they do not influence behaviour, i.e. they are neglected.10

**Elements of risk**

Risk has two elements:

- The likelihood or probability of an adverse event
- Its severity.

In medical practice in general, concern ceases when risks fall below about 1 in 100 000 instances, when the procedure then is regarded as ‘safe’. In such cases, when disaster occurs, it can be difficult indeed for individuals to accept that they ‘deliberately’ accepted a risk; they feel ‘it should not have happened to me’ and in their distress they may seek to lay blame on others where there is no fault or negligence, only misfortune (see Warnings and consent).

---

9This phrase is commonly used in the context of motor vehicle accidents, but applies equally well to the prescribing of drugs.

10Sometimes the term minimal risk is used to mean risk about equal to going about our ordinary daily lives; it includes travel on public transport, but not motor bicycling on a motorway.
The benefits of chemicals used to colour food verge on or even attain negligibility, although some cause allergy in humans. Our society permits their use. There is general agreement that drugs prescribed for disease are themselves the cause of a significant amount of disease (adverse reactions), of death, of permanent disability, of recoverable illness and of minor inconvenience. In one major UK study the prevalence of adverse drug reactions as a cause of admission to hospital was 6.5% (see p. 000 for other examples).

**Three major grades of risk**
These are: unacceptable, acceptable and negligible. Where disease is life-threatening and there is reliable information on both the disease and the drug, then decisions, though they may be painful, present relatively obvious problems. But where the disease risk is remote, e.g. mild hypertension, or where drugs are to be used to increase comfort or to suppress symptoms that are, in fact, bearable, or for convenience rather than for need, then the issues of risk acceptance are less obvious.

Risks should not be weighed without reference to benefits any more than benefits should be weighed without reference to risks.

Risks are among the facts of life. In whatever we do and in whatever we refrain from doing, we are accepting risk. Some risks are obvious, some are unsuspected and some we conceal from ourselves. But risks are universally accepted, whether willingly or unwillingly, whether consciously or not.¹¹

**Whenever a drug is taken a risk is taken**
The risk comprises the properties of the drug, the prescriber, the patient and the environment; it is often so small that second thoughts are hardly necessary, but sometimes it is substantial. The doctor must weigh the likelihood of gain for the patient against the likelihood of loss. There are often insufficient data for a rational decision to be reached, but a decision must yet be made, and this is one of the greatest difficulties of clinical practice. Its effect on the attitudes of doctors is often not appreciated by those who have never been in this situation. The patient’s protection lies in the doctor’s knowledge of the drug and of the disease, and experience of both, together with knowledge of the patient.

We continue to use drugs that are capable of killing or disabling patients at doses within the therapeutic range where the judgement of overall balance of benefit and risk is favourable. This can be very difficult for the patient who has suffered a rare severe adverse reaction, to understand and to accept (see below).

In some chronic diseases that ultimately necessitate suppressive drugs, the patient may not experience benefit in the early stages. Patients with early Parkinson’s disease may experience little inconvenience or hazard from the condition, and premature exposure to drugs can exact such a price in unwanted effects that they prefer the untreated state. What patients will tolerate depends on their personality, their attitude to disease, their occupation, mode of life and relationship with their doctor (see Compliance, p. 000).

**PUBLIC VIEW OF DRUGS AND PRESCRIBERS**
The current public view of modern medicines, ably fuelled by the mass media, is a compound of vague expectation of ‘miracle’ cures with outrage when anything goes wrong. It is also unreasonable to expect the public to trust the medical profession (in collaboration with the pharmaceutical industry) to the extent of leaving to them all drug matters.

The public wants benefits without risks and without having to alter its unhealthy ways of living; this is a deeply irrational position. But it is easy to understand that a person who has taken into their body a chemical with intent to relieve suffering, whether or not it is self-induced, can feel profound anger when harm ensues. Expectations are high, and now, at the beginning of the 21st century, with the manifest achievement of technology all around us, the expectation that happiness can be a part of the technological package must yet be seen as naive and unrealisable.

Patients are aware that there is justifiable criticism of the standards of medical prescribing – indeed, doctors are in the forefront of this – as well as justifiable criticism of promotional practices of the profitably rich, aggressive, international pharmaceutical industry.

There are obvious areas where some remedial action is possible:

Maintaining high standards of prescribing by doctors, including better communication with patients, i.e. doctors must learn to feel that introduction of foreign chemicals into their patients’ bodies is a serious matter, which the majority do not seem to feel at present.

Introduction of no-fault compensation schemes for serious drug injury (some countries already have these).

Informed public discussion of the issues between the medical profession, industrial drug developers, politicians and other ‘opinion formers’ in society, and patients (the public).

Restrain in promotion by the pharmaceutical industry, including self-control by both industry and doctors in their necessarily close relationship, which the public is inclined to regard as a conspiracy.

If restraint by both parties is not forthcoming, and it may not be, then both doctor and industry can expect the exercise of more control over them by politicians responding to public demand.

CRITICISMS OF MODERN DRUGS

Extremist critics have attracted public attention for their view that modern drug therapy, indeed modern medicine in general, does more harm than good; others, whilst admitting some benefits from drugs, insist that this is medically marginal.

These opinions rest on the undisputed fact that favourable trends in many diseases preceded the introduction of modern drugs and were due to economic and environmental changes, sanitation, nutrition and housing. They also rest on the claim that drugs have not changed expectation of life or mortality (as measured by national mortality statistics), and that drugs can cause illness (adverse reactions).

If something is to be measured then the correct criteria must be chosen. Overall mortality figures are an extremely crude and often an irrelevant measure of the effects of drugs whose major benefits are so often on quality of life rather than on its quantity.

Two examples of inappropriate measurements will suffice:

1. In the case of many infections, environmental changes have had an indisputably greater beneficial effect on health than the subsequently introduced antimicrobials. But this does not mean that environmental improvements alone are sufficient in the fight against infections. When comparisons of illnesses in the pre- and post-antimicrobial eras are made, like is not compared with like. Environmental changes achieved their results when the mortality rate from infections was high and antimicrobials were not available; antimicrobials came later, against a background of low mortality as well as of environmental change; decades separate the two parts of the comparison, and observers, diagnostic criteria and data recording changed during this long period. It is evident that determining the value of antimicrobials is not simply a matter of looking at mortality rates.

2. About 1% of the UK population has diabetes mellitus and about 1% of death certificates mention diabetes. This is no surprise because all must die and insulin is no cure for this lifelong disease. A standard medical textbook of 1907 stated that juvenile-onset ‘diabetes is in all cases a grave disease, and the subjects are regarded by all assurance companies as uninsurable lives: life seems to hang by a thread, a thread often cut by a very trifling accident’. Most, if not all, life insurance companies now accept young people with diabetes with no or only modest financial penalty – the premium of a person 5–10 years older. Before insulin replacement therapy was available few survived beyond 3 years after diagnosis, they died for lack of insulin. It is unjustified to assert that a treatment is worthless just because its mention on death certificates (whether as a prime or as a contributory cause) has not declined. The relevant criteria for juvenile-onset diabetes are change in the age at which the subjects die and the quality of life between diagnosis and death, and both of these have changed enormously.

12 A cure eliminates a disease and may be withdrawn when this is achieved.

13 Even if given the best treatment. ‘Opium alone stands the test of experience as a remedy capable of limiting the progress of the disease’, wrote the great Sir William Osler, successively Professor of Medicine in Pennsylvania, McGill, Johns Hopkins and Oxford Universities, in 1918, only 3 years before the discovery of insulin.
PHYSICIAN-INDUCED (IATROGENIC) DISEASE

They used to have a more equitable contract in Egypt: for the first three days the doctor took on the patient at the patient's risk and peril; when the three days were up, the risks and perils were the doctor's.

But doctors are lucky: the sun shines on their successes and the earth hides their failures.  

It is a salutary thought that each year medical errors kill an estimated 44 000 to 98 000 Americans (more than die in motor vehicle accidents) and injure 1 000 000.  

Among inpatients in the USA and Australia, about half of the injuries caused by medical mismanagement result from surgery, but therapeutic mishaps and diagnostic errors are the next most common. In one survey of adverse drug events, 1% were fatal, 12% life-threatening, 30% serious and 57% significant.  

About half of the life-threatening and serious events were preventable. Errors of prescribing account for one-half and those of administering drugs for one-quarter of these. Inevitably, a proportion of lapses result in litigation, and in the UK 20–25% of complaints received by the medical defence organisations about general practitioners follow medication errors.

The most shameful act in therapeutics, apart from actually killing a patient, is to injure a patient who is but little disabled or who is suffering from a self-limiting disorder. Such iatrogenic disease, induced by misguided treatment, is far from rare.

Doctors who are temperamentally extremist will do less harm by therapeutic nihilism than by optimistically overwhelming patients with well intentioned poly-pharmacy. If in doubt whether or not to give a drug to a person who will soon get better without it, don't.

In 1917 the famous pharmacologist, Sollmann, felt able to write:

Pharmacology comprises some broad conceptions and generalisations, and some detailed conclusions, of such great and practical importance that every student and practitioner should be absolutely familiar with them. It comprises also a large mass of minute details, which would constitute too great a tax on human memory, but which cannot safely be neglected.

The doctor's aim must be not merely to give the patient what will do good, but to give only what will do good, or at least more good, than harm. The information explosion of recent decades is now under better control such that prescribers can, from their desktop computer terminals, enter the facts about their patient (age, sex, weight, principal and secondary diagnoses) and receive suggestions for which drugs should be considered, with proposed doses and precautions.

DRUG-INDUCED INJURY (see also Chapter 8)

Responsibility for drug-induced injury raises important issues affecting medical practice and development of needed new drugs, as well as of law and of social justice.

Negligence and strict and no-fault liability

All civilised legal systems provide for compensation to be paid to a person injured as a result of using a product of any kind that is defective due to negligence (fault is a failure to exercise reasonable care).  

But there is a growing opinion that special compensation for serious personal injury, beyond the modest sums that general social security systems provide, should be automatic and not dependent on fault and proof of fault of the producer, i.e. there

---

15Kohn L, Corrigan J, Donaldson M (eds) for the Committee on Quality of Health Care in America, Institute of Medicine 2000 To err is human: building a safer health system. National Academy Press, Washington, DC.  
17Iatrogenic means ‘physician-caused’, i.e. disease consequent on following medical advice or intervention (from the Greek iatros, physician).  
19This discussion is about drugs that have been properly manufactured and meet proper standards, e.g. of purity, stability, as laid down by regulatory bodies or pharmacopoeias. A manufacturing defect would be dealt with in a way no different from manufacturing errors in other products.  
20A plaintiff (person who believes he or she has been injured) seeking to obtain compensation from a defendant (via the law of negligence) must prove three things: (1) that the defendant owed a duty of care to the plaintiff; (2) that the defendant failed to exercise reasonable care; and (3) that the plaintiff has suffered actual injury as a result.
should be ‘liability irrespective of fault’, ‘no-fault liability’ or ‘strict liability’.\(^{21}\)

Many countries are now revising their laws on liability for personal injury due to manufactured products and are legislating Consumer Protection Acts (Statutes) that include medicines, for ‘drugs represent the class of product in respect of which there has been the greatest pressure for surer compensation in cases of injury’.\(^{22}\)

Issues that are central to the debate include:

- **Capacity to cause harm** is inherent in drugs in a way that sets them apart from other manufactured products; and harm often occurs in the absence of fault.
- **Safety**, i.e. the degree of safety that a person is entitled to expect, and adverse effects that should be accepted without complaint, must often be a matter of opinion and will vary with the disease being treated, e.g. cancer or insomnia.
- **Causation**, i.e. proof that the drug in fact caused the injury, is often impossible, particularly where it increases the incidence of a disease that occurs naturally.
- **Contributory negligence**. Should compensation be reduced in smokers and drinkers where there is evidence that these pleasure-drugs increase liability to adverse reactions to therapeutic drugs?
- **The concept of defect**, i.e. whether the drug or the prescriber or indeed the patient can be said to be ‘defective’ so as to attract liability, is a highly complex matter and indeed is a curious concept as applied to medicine.

A scheme that meets all the major difficulties has not yet been implemented anywhere. This is not because there has been too little thought; it is because the subject is difficult. Nevertheless, no-fault schemes operate in New Zealand, Scandinavia and France.\(^{23}\) The following principles might form the basis of a workable compensation scheme for injury due to drugs:

- **New unlicensed drugs undergoing clinical trial in small numbers of subjects** (healthy or patient volunteers): the developer should be strictly liable for all adverse effects.
- **New unlicensed drugs undergoing extensive trials in patients who may reasonably expect benefit**: the producer should be strictly liable for any serious effect.
- **New drugs after licensing by an official body**: the manufacturer and the community should share liability for serious injury, as new drugs provide general benefit. An option might be to institute a defined period of formal prospective drug surveillance monitoring, in which both doctors and patients agree to participate.
- **Standard drugs in day-to-day therapeutics**:

1. There should be a no-fault scheme, operated by or with the assent of government that has authority, through tribunals, to decide cases quickly and to make awards. This body would have authority to reimburse itself from others – manufacturer, supplier, prescriber – wherever that was appropriate. An award must not have to wait on the outcome of prolonged, vexatious, adversarial, expensive court proceedings.

2. Patients would be compensated where:
   - causation was proven on ‘balance of probability’\(^{24}\)
   - the injury was serious
   - the event was rare and remote and not reasonably taken into account in making the decision to treat.

Practitioners of complementary and alternative medicine (CAM)\(^{25}\) are severely critical of modern...
drugs, and use practices according to their own special beliefs. It is appropriate therefore to discuss such medical systems here.

The term ‘complementary and alternative’ medicine covers a broad range of heterogeneous systems of therapy (from acupuncture to herbalism to yoga), and diagnosis (from bioresonance to pulse and tongue diagnosis). The present discussion relates largely to CAM but recognises that traditional or indigenous medicinal therapeutics has developed since before history in all societies. This comprises a mass of practices varying from the worthless to highly effective remedies, e.g. digitalis (England), quinine (South America), reserpine (India), atropine (various countries). It is the task of science to find the gems and to discard the dross, and at the same time to leave intact socially valuable supportive aspects of traditional medicine.

There is no doubt that the domain of CAM has grown in popularity in recent years; a survey estimated that about 20% of the UK population had consulted a CAM practitioner in the previous year. In Germany, the figure exceeds 60%, with $2.06 billion in over-the-counter sales in 2003. Usage rises sharply among those with chronic, relapsing conditions such as cancer, multiple sclerosis, human immunodeficiency virus (HIV) infection, psoriasis and rheumatological diseases. It is difficult to resist the conclusion that when scientific medicine neither guarantees happiness nor wholly eliminates the disabilities of degenerative diseases in long-lived populations, and when drugs used in modern medicine cause serious harm, public disappointment naturally leads to a revival of interest in alternatives that alluringly promise efficacy with complete safety. These range from a revival of traditional medicine to adoption of the more modern cults. Features common to medical cults: are absence of scientific thinking, naïve acceptance of hypotheses, uncritical acceptance of causation, e.g. reliance on anecdote or opinion (as opposed to evidence), assumption that if recovery follows treatment it is due to the treatment, and close attention to the patient’s personal feelings. Lack of understanding of how therapeutic effects may be measured is also a prominent feature. An extensive analysis of recommendations of CAM therapies for specific medical conditions from seven textbook sources revealed numerous treatments recommended for the same condition, for example: addictions (120 treatments recommended), arthritis (121), asthma (119) and cancer (133), but there was lack of agreement between these authors as to the preferred therapies for specified conditions. The question must arise that if numerous and heterogeneous treatments are effective for the same condition, could they not have some common feature, such as the ability of the practitioner to inspire confidence in the patient?

---

26Traditional medicine is fostered particularly in countries where scientific medicine is not accessible to large populations for economic reasons, and destruction of traditional medicine would leave unhappy and sick people with nothing. For this reason, governments are supporting traditional medicine and at the same time initiating scientific clinical evaluations of the numerous plants and other items employed, many of which contain biologically active substances. The World Health Organization is supportive to these programmes.


29A cult is a practice that follows a dogma, tenet or principle based on theories or beliefs of its promulgator to the exclusion of demonstrable scientific experience (definition of the American Medical Association). Scientific medicine changes in accord with evidence obtained by scientific enquiry applied with such intellectual rigour as is humanly possible. But this is not the case with cults, the claims for which are characterised by absence of rigorous intellectual evaluation and unchangeability of beliefs. The profusion of medical cults prompts the question why, if each cult has the efficacy claimed by its exponents, conventional medicine and indeed the other cults are not swept away. Some practitioners use conventional medicine and, where it fails, turn to cult practices. Where such complementary practices give comfort they are not to be despised, but their role and validity should be clearly defined. No community can afford to take these cults at their own valuation; they must be tested, and tested with at least the rigour required to justify a therapeutic claim for a new drug. It is sometimes urged in extenuation that traditional and cult practices do no harm to patients, unlike synthetic drugs. But, even if that were true (which it is not), investment of scarce resources in delivering what may be ineffective, though sometimes pleasing, experiences, e.g. dance therapy, exaltation of flowers and the admittedly inexpensive urine therapy, means that resources are not available for other desirable social objectives, e.g. housing, art subsidies, medicine. We do not apologise for this diversion to consider medical cults and practices, for the world cannot afford unreason, and the antidote to unreason is reason and the rigorous pursuit of knowledge, i.e. evidence-based medicine.

A scientific approach does not mean treating a patient as a mere biochemical machine. It does not mean the exclusion of spiritual, psychological and social dimensions of human beings. But it does mean treating these in a rational manner.

Some common false beliefs of CAM practitioners are that synthetic modern drugs are toxic, but products obtained in nature are not.31 Scientific medicine is held to accept evidence that remedies are effective only where the mechanism is understood, that it depends on adherence to rigid and unalterable dogmas, and recognises no form of evaluation other than the strict randomised controlled trial. Traditional (pre-scientific) medicine is deemed to have special virtue, and the collection and formal analysis of data on therapeutic outcomes, failures as well as successes, is deemed inessential. There is also a tenet that if patient gets better when treated in accordance with certain beliefs, this provides evidence for the truth of these beliefs (the post hoc ergo propter hoc32 fallacy).

Exponents of CAM often state that comparative controlled trials of their medicines against conventional medicines are impracticable because the classic double-blind randomised controlled designs are inappropriate and in particular do not allow for the individual approach characteristic of complementary medicine. But modern therapeutic trial designs can cope with this. There remain extremists who contend that they understand scientific method, and reject it as invalid for what they do and believe, i.e. their beliefs are not, in principle, refutable. This is the position taken up by magic and religion where subordination of reason to faith is a virtue.

CAM particularly charges that conventional medicine seriously neglects patients as whole integrated human beings (body, mind, spirit) and treats them too much as machines. Conventional practitioners may well feel uneasily that there has been and still is truth in this, that with the development of specialisation some doctors have been seduced by the enormous successes of medical science and technology and have become liable to look too narrowly at their patients where a much broader (holistic) approach is required. It is evident that such an approach is likely to give particular satisfaction in psychological and psychosomatic conditions for which conventional doctors in a hurry have been all too ready to think that a prescription meets all the patients’ needs.

CAM does not compete with the successful mainstream of scientific medicine. Users of CAM commonly have chronic conditions and have tried conventional medicine but found that it has not offered a satisfactory solution, or has caused adverse effects. The problems, when they occur, are often at the interface between CAM and mainstream medicine. A doctor prescribing a conventional medicine

---

31Black cohosh (Cimicifuga racemosa), taken for hot flushes and other menopausal symptoms (but no better than placebo in clinical trial), can cause serious liver disorder. Herbal teas containing pyrrolizidine alkaloids (Senecio, Crotalaria, Heliotropium) cause serious hepatic veno-occlusive disease. Comfrey (Symphytum) is similar but also causes hepatocellular tumours and haemangiomias. Sassafras (carminative, antiarheumatic) is hepatotoxic. Mistletoe (Viscum) contains cytotoxic alkaloids. Ginseng contains oestrogenic substances that have caused gynaecomastia; long-term users may show ‘ginseng abuse syndrome’ comprising central nervous system excitation; arterial hypertension can occur. Liquorice (Glycyrrhiza) has mineralocorticoid action. An amateur ‘health food enthusiast’ made himself a tea from ‘an unfamiliar [to him] plant’ in his garden: unfortunately this was the familiar foxglove (Digitalis purpurea); he became very ill, but happily recovered. Other toxic natural remedies include lily of the valley (Convallaria) and horse chestnut (Aesculus). ‘The medical herbalist is at fault for clinging to outworn historical authority and for not assessing his drugs in terms of today’s knowledge, and the orthodox physician is at fault for a cynical scepticism with regard to any healing discipline other than his own’ (Penn R G 1983 Adverse reactions to herbal medicines. Adverse Drug Reaction Bulletin 102:376–379). The Medicines and Healthcare products Regulatory Agency provides advice at: http://www.mhra.gov.uk.

---

32Latin: after this; therefore on account of this.
may be unaware that a patient is taking herbal medicine, and there is ample scope for unwanted herb-drug interaction by a variety of mechanisms. These include:

- **CYP450 enzyme induction** – St John’s wort (by reducing the plasma concentration or therapeutic efficacy of warfarin, ciclosporin, simvastatin, oral contraceptives)
- **CYP450 enzyme inhibition** – piperine (by increasing plasma concentrations of propranolol and theophylline)
- **Additive action** – St John’s wort on serotonin-specific reuptake inhibitors (by increasing their unwanted effects).

More troubling is the issue of conflicting advice between CAM and mainstream drugs, as witnessed by the advice to travellers from some homoeopathic pharmacies to use their products for malaria prophylaxis in place of conventional drugs (an action that drew criticism from the Society of Homoeopaths).

Regulations being introduced by European Union Directive (and voluntarily in the UK) will move towards formal registration of practitioners of some forms of CAM (notably herbal medicines), according to agreed standards of qualification.

The following will suffice to give the flavour of homoeopathy, the principal complementary medicine system involving medicines, and the kind of criticism with which it has to contend.

**HOMOEOPATHY**

Homoeopathy is a system of medicine founded by Samuel Hahnemann (German physician, 1755–1843) and expounded by him in the ‘Organon of the Rational Art of Healing’. Hahnemann described his position:

After I had discovered the weakness and errors of my teachers and books I sank into a state of sorrowful indignation, which had nearly disgusted me with the study of medicine. I was on the point of concluding that the whole art was vain and incapable of improvement. I gave myself up to solitary reflection, and resolved not to terminate my train of thought until I had arrived at a definite conclusion on the subject.

By understandable revulsion at the medicine of his time, by experimentation on himself (a large dose of quinine made him feel as though he had a malarial attack) and by search of records he ‘discovered’ a ‘law’ that is central to homoeopathy, and from which the name is derived (cf. **allopathy**, p. 000):

> Similar symptoms in the remedy remove similar symptoms in the disease. The eternal, universal law of Nature, that every disease is destroyed and cured through the similar artificial disease which the appropriate remedy has the tendency to excite, rests on the following proposition: that only one disease can exist in the body at any one time.

In addition to the above, Hahnemann ‘discovered’ that dilution potentiates the effect of drugs, but not of trace impurities (provided the dilution is shaken correctly, i.e. by ‘succussion’), even to the extent that an effective dose may not contain a single molecule of the drug. It has been pointed out that the ‘thirtieth potency’ (1 in 10\(^{60}\)), recommended by Hahnemann, provided a solution in which there would be one molecule of drug in a volume of a sphere of literally astronomical circumference.

The therapeutic efficacy of a dilution at which no drug is present (including sodium chloride prepared in this way) is explained by the belief that a spiritual energy diffused throughout the medicine by the particular way in which the dilutions are shaken (succussion) during preparation, or that the active molecules leave behind some sort of ‘imprint’ on solvent or excipient. The absence of potentiation of the inevitable contaminating impurities is attributed to the fact that they are not incorporated by serial dilution.

Thus, writes a critic:

> We are asked to put aside the whole edifice of evidence concerning the physical nature of materials and the normal concentration–response relationships of biologically active substances in order to accommodate homoeopathic potency.

---


\(^{14}\)Greek: *hemos* = same; *patheia* = suffering.

But no hard evidence that tests the hypothesis is supplied to justify this, and we are invited, for instance, to accept that sodium chloride merely diluted is no remedy, but that ‘it raises itself to the most wonderful power through a well prepared dynamisation process’ and stimulates the defensive powers of the body against the disease.

Pharmacologists have felt, in the absence of conclusive evidence from empirical studies that homeopathic medicines can reproducibly be shown to differ from placebo, that there is no point in discussing its hypotheses.40 But empirical studies can be made without accepting any particular theory of causation; nor should the results of good studies be disregarded just because the proposed theory of action seems incredible or is unknown.

A meta-analysis of 186 double-blind and/or randomised placebo-controlled trials of homeopathic remedies found that 89 had adequate data for analysis. The authors concluded that their results ‘were not compatible with the hypothesis that the clinical effects are completely due to placebo’, but also found ‘insufficient evidence from these studies that homoeopathy is clearly efficacious for any single clinical condition’.41 A subsequent analysis of 110 homeopathic and 110 conventional medicine trials found that there was ‘weak evidence for a specific effect of homeopathic remedies, but strong evidence for a specific effect of conventional interventions.’ The authors concluded: ‘This finding is compatible with the notion that the clinical effects of homoeopathy are placebo effects.’42 These studies evoked strong reactions from practitioners of homoeopathy and others, but they raise the possibility that patients’ reactions to homoeopathy, and indeed some other forms of CAM, may rest within an understanding of the complex nature of the placebo response and, in particular, its biology (see below).

CONCLUSION

There is a single fundamental issue between conventional scientific medicine and traditional, complementary and alternative medicine (although it is often obscured by detailed debates on individual practices); the issue is: what constitutes acceptable evidence, i.e. what is the nature, quality and interpretation of evidence that can justify general adoption of modes of treatment and acceptance of hypotheses? When there is agreement that a CAM treatment works, it becomes conventional and, in respect of that treatment, there is no difference between CAM and orthodox scientific medicine.

In the meantime, we depend on the accumulation of evidence from empirical studies to justify the allocation of resources for future research.

PLACEBO MEDICINES

A placebo43 is any component of therapy that is without specific biological activity for the condition being treated.

Placebo medicines are used for two purposes:

- As a control in scientific evaluation of drugs (see Therapeutic trials, p. 000)
- To benefit or please a patient, not by any pharmacological actions, but by psychological means.

All treatments have a psychological component, whether to please (placebo effect) or, occasionally, to vex (negative placebo or nocebo44 effect).

---

40 Editorial 1988 When to believe the unbelievable. Nature 333:787. A report of an investigation into experiments with antibodies in solutions that contained no antibody molecules (as in some homeopathic medicines). The editor of Nature took a three-person team (one of whom was a professional magician, included to detect any trickery) on a week-long visit to the laboratory that claimed positive results. Despite the scientific seriousness of the operation, it developed comical aspects (codes of the contents of test tubes were taped to the laboratory ceiling); the Nature team, having reached an unfavourable view of the experiments, ‘sped past the [laboratory] common-room filled with champagne bottles destined now not to be opened’. Full reports in this issue of Nature (28 July 1988), including an acrimonious response by the original scientist, are highly recommended reading, both for scientific logic and for entertainment. See also Nature (1994) 370:322.


43 Latin: placebo = shall be pleasing or acceptable. For a comment on its historical use, see Edwards M 2005 Lancet 365:1023.

44 Latin: nocebo = shall injure; the term is little used.
A placebo medicine is a vehicle for ‘cure’ by suggestion, and is surprisingly often successful, if only temporarily. All treatments carry a placebo effect – physiotherapy, psychotherapy, surgery, entering a patient into a therapeutic trial, even the personality and style of the doctor – but the effect is most easily investigated with drugs, for the active and the inert can often be made to appear identical to allow comparisons.

The deliberate use of drugs as placebos is a confession of therapeutic failure by the doctor. Failures, however, are sometimes inevitable and an absolute condemnation of the use of placebos on all occasions would be unrealistic.

**Placebo-reactors** are suggestible people who are likely to respond favourably to any treatment. They have misled doctors into making false therapeutic claims.

**Negative reactors**, who develop adverse effects when given a placebo, exist but, fortunately, are fewer.

Some 30–80% of patients with chronic stable angina pectoris and 30–50% with depression respond to placebos. Placebo reaction is an inconsistent attribute: a person may respond at one time in one situation and not at another time under different conditions. In one study on medical students, psychological tests revealed that those who reacted to a placebo tended to be extroverted, sociable, less dominant, less self-confident, more appreciative of their teaching, more aware of their autonomic functions and more neurotic than their colleagues who did not react to a placebo under the particular conditions of the experiment.

Modern brain-scanning techniques provide evidence that the placebo effect has a physiological basis. Positron emission tomography showed that both opioid and placebo analgesia were associated with increased activity in the same cortical area of the brain, the greatest responses occurring in high placebo responders. Functional magnetic resonance imaging demonstrated that strong cortical activation correlated with greater placebo-induced pain relief.

It is important that all who administer drugs should be aware that their attitudes to the treatment may greatly influence the outcome. Undue scepticism may prevent a drug from achieving its effect, and enthusiasm or confidence may potentiate the actions of drugs.

**Tonics** are placebos. They may be defined as substances that aspire to strengthen and increase the appetite of those so weakened by disease, misery, overindulgence in play or work, or by physical or mental inadequacy, that they cannot face the stresses of life. The essential feature of this weakness is the absence of any definite recognisable defect for which there is a known remedy. As tonics are placebos, they must be harmless.

---

45 As the following account by a mountain rescue guide illustrates: ‘The incident involved a 15-year-old boy who sustained head injuries and a very badly broken leg. Helicopter assistance was unavailable and therefore we had to carry him by stretcher to the nearest landrover (several miles away) and then on to a waiting ambulance. During this long evacuation the boy was in considerable distress and we administered Entonox (a mixture of nitrous oxide and oxygen, 50% each) sparingly as we only had one small cylinder. He repeatedly remarked how much better he felt after each intake of Entonox (approximately every 20 minutes) and after 7 hours or so, we eventually got him safely into the ambulance and on his way to hospital. When going to replace the Extonox we discovered the cylinder was still full of gas due to the equipment being faulty. There was no doubt that the boy felt considerable pain relief because he thought he was receiving Entonox.’


48 Tonics (licensed) available in the UK include: Gentian Mixture, acid (or alkaline) (gentian, a natural plant bitter substance, and dilute hydrochloric acid or sodium bicarbonate); Labiton (thiamine, caffeine, alcohol, all in low dose).
Drugs can interact, producing a positive adverse effect or a negative adverse effect, i.e. therapeutic failure.

Drugs can give diagnostic clues, e.g. ampicillin and amoxicillin causing rash in infectious mononucleosis – a diagnostic adverse effect, not a diagnostic test.

Drugs can cause false results in clinical chemistry tests, e.g. plasma cortisol, urinary catecholamine, urinary glucose.

Drug history can assist choice of drugs in the future.

Drugs can leave residual effects after administration has ceased, e.g. chloroquine, amiodarone.

Drugs available for independent patient self-medication are increasing in range and importance.

Appropriate prescribing is that which bases the choice of a drug on its effectiveness, safety and convenience relative to other drugs or treatments (e.g. surgery or psychotherapy), and considers cost only when those criteria for choice have been satisfied. In some circumstances appropriateness will require the use of more costly drugs. Only by giving appropriateness high priority will health payers be able to achieve their aim of ensuring that patients’ clinical needs will be met (Report).

Prescribing should be appropriate:

1. Generic substitution, where a generic formulation (see p. 000) is substituted (by a pharmacist) for the proprietary formulation prescribed by the doctor.

2. Therapeutic substitution, where a drug of different chemical structure is substituted for the drug prescribed by the doctor. The substitute is of the same chemical class and is deemed to have similar pharmacological properties and to give similar therapeutic benefit. Therapeutic substitution is a particularly controversial matter where it is done without consulting the prescriber, and legal issues may be raised in the event of adverse therapeutic outcome.

The following facts and opinions are worth some thought:

- UK National Health Service (NHS) spending on drugs has been 9–11% per year (of the total cost) for nearly 50 years.
- General practitioners (i.e. primary care) spend some 80% of the total cost of drugs.
- In the past 25 years, the number of NHS prescriptions has risen from 5.5 to over 13 per person.
The average cost per head of medicines supplied to people aged over 75 years is nearly five times that of medicines supplied to those below pensionable age (in the UK: women 62 years, men 65 years, but under revision).

Underprescribing can be just as harmful to the health of patients as overprescribing.

It is crucially important that incentives and sanctions address quality of prescribing as well as quantity: ‘it would be wrong if too great a preoccupation with the cost issue in isolation were to encourage under-prescribing or have an adverse effect on patient care’ (Report).

Reasons for underprescribing include: lack of information or lack of the will to use available information (in economically privileged countries there is, if anything, a surplus of information); fear of being blamed for adverse reactions (affecting doctors who lack the confidence that a knowledge of pharmacological principles confers); fear of sanctions against over-costly prescribing. Prescription frequency and cost per prescription are lower for older than for younger doctors. There is no evidence that the patients of older doctors are worse off as a result.

REPEAT PRESCRIPTIONS

About two-thirds of general (family) practice prescriptions are for repeat medication (half issued by the doctor at a consultation and half via the practice nurse or receptionist without patient contact with the doctor). Some 95% of patients’ requests are acceded to without further discussion; 25% of patients who receive repeat prescriptions have had 40 or more repeats; and 55% of patients aged over 75 years are on repeat medication (with periodic review).

Many patients taking the same drug for years are doing so for the best reason, i.e. firm diagnosis for which effective therapy is available, such as epilepsy, diabetes, hypertension, but some are not.

WARNINGS AND CONSENT

Doctors have a professional duty to inform and to warn, so that patients, who are increasingly informed and educated, may make meaningful personal choices, which it is their right to do (unless they opt to leave the choice to the doctor, which it is also their right). Patients now have access to a potentially confusing quantity of detail about the unwanted effects of drugs (information sheet, the internet, the media) but without the balancing influence of data on their frequency of occurrence. It would be prudent for doctors to draw attention at least to adverse effects that are common, serious (even if uncommon), or avoidable or mitigated if recognised.

Warnings to patients are of two kinds:

- Warnings that will affect the patient’s choice to accept or reject the treatment
- Warnings that will affect the safety of the treatment once it has begun, e.g. risk of stopping treatment, occurrence of drug toxicity.

Just as engineers say that the only safe aeroplane is the one that stays on the ground in still air on a disused airfield or in a locked hangar, so the only safe drug is one that stays in its original package. If drugs are not safe then plainly patients are entitled to be warned of their hazards, which should be explained to them, i.e. probability, nature and severity.

There is no formal legal or ethical obligation on doctors to warn all patients of all possible adverse consequences of treatment. It is their duty to adapt the information they give (not too little, and not so much as to cause confusion) so that the best interest of each patient is served. If there is a ‘real’ (say 1–2%) risk inherent in a procedure of some misfortune occurring, then doctors should warn patients of the possibility that the injury may occur, however well the treatment is performed. Doctors should take into account the personality of the patient, the likelihood of any misfortune arising and what warning was necessary for each particular patient’s welfare.

Doctors should consider what their particular individual patients would wish to know (i.e. would be likely to attach significance to) and not only what they think (paternalistically) the patients ought to know. It is part of the professionalism of doctors to tell what is appropriate to the individual patient’s interest. If things go wrong doctors must be prepared to defend what they did or, more important in the case of warnings, what they did not do, as being in their patient’s best interest. Courts of law will look critically at doctors who seek to justify under-information by saying that they feared to confuse or...
frighten the patient (or that they left it to the patient to ask, as one doctor did). The increasing availability of patient information leaflets (PILs) prepared by the manufacturer indicates the increasing trend to give more information. Doctors should know what their patients have read (or not read, as is so often the case) when patients express dissatisfaction.

Evidence that extensive information on risks causes 'unnecessary' anxiety or frightens patients suggests that this is only a marginal issue and it does not justify a general policy of withholding of information.

LEGAL HAZARDS FOR PRESCRIBERS

Doctors would be less than human if, as well as trying to help their patients, they were not also concerned to protect themselves from allegations of malpractice (negligence). A lawyer specialising in the field put the legal position regarding a doctor's duty pungently:

The provision of information to patients is treated by (English) law as but one part of the way a doctor discharges the obligation he owes to a patient to take reasonable care in all aspects of his treatment of that patient. The provision of information is a corollary of the patient's right to self-determination which is a right recognised by law. Failure to provide appropriate information will usually be a breach of duty and if that breach leads to the patient suffering injury then the basis for a claim for compensation exists. 51

The keeping of appropriate medical records, written at the time of consultation (and which is so frequently neglected), is not only good medical practice, it is the best way of ensuring that there is an answer to unjustified allegations, made later, when memory has faded. At the very least, these should include records of warning about treatments that are potentially hazardous.

FORMULARIES, GUIDELINES AND ‘ESSENTIAL’ DRUGS

Increasingly, doctors recognise that they need guidance through the bountiful menu (thousands of medicines) so seductively served to them by the pharmaceutical industry. Principal sources of guidance are the pharmaceutical industry (‘prescribe my drug’) and governments (‘spend less’), and also the developing (profit-making) managed care/insurance bodies (‘spend less’) and the proliferating drug bulletins offering independent, and supposedly unbiased advice (‘prescribe appropriately’).

Even the pharmaceutical industry, in its more sober moments, recognises that their ideal world in which doctors, advised and informed by industry alone, were free to prescribe whatever they pleased, to whomsoever they pleased, for as long as they pleased with someone other than the patient paying, is an unrealisable dream of a ‘never-never land’.

The industry knows that it has to learn to live with restrictions of some kinds and one of the means of restriction is the formulary, a list of formulations of medicines with varying amounts of added information. A formulary may list all nationally licensed medicines prescribable by health professionals, or list only preferred drugs.

It may be restricted to what a third-party payer will reimburse, or to the range of formulations stocked in a hospital (and chosen by a local drugs and therapeutics committee, which all hospitals or groups of hospitals should have), or the range agreed by a partnership of general practitioners or primary care health centre.

All restricted formularies are heavily motivated to keep costs down without impairing appropriate prescribing (see p. 000). They should make provision for prescribing outside their range in cases of special need with an ‘escape clause’.

Thus, restricted formularies are in effect guidelines for prescribing. There is a profusion of these from national sources, hospitals, group practices and specialty organisations (epilepsy, diabetes mellitus).

‘Essential’ drugs

Economically disadvantaged countries may seek help to construct formularies. Technical help comes

51Ian Dodds-Smith.
from the World Health Organization (WHO) with its Model List of Essential Medicines,\textsuperscript{53} i.e. drugs (or representatives of classes of drugs) ‘that satisfy the health care needs of the majority of the population; they should therefore be available at all times in adequate amounts and in the appropriate dosage forms’. Countries seeking such advice can use the list as a basis for their own choices (the WHO also publishes model prescribing information).\textsuperscript{54} The list, updated regularly, contains about 300 items.

The pharmaceutical industry dislikes the concept of drugs classed as essential as others, by implication, are judged inessential. But the WHO programme has attracted much interest and approval (see WHO Technical Report Series: The use of essential drugs: current edition).

**COMPLIANCE**

Successful therapy, especially if it is long term, comprises a great deal more than choosing a standard medicine. It involves patient and doctor compliance.\textsuperscript{55} The latter is liable to be overlooked (by doctors), for doctors prefer to dwell on the deficiencies of their patients rather than of themselves.

**PATIENT COMPLIANCE**

Patient compliance is the extent to which the actual behaviour of the patient coincides with medical advice and instructions; it may be complete, partial, erratic, nil, or there may be over-compliance. To make a diagnosis and to prescribe evidence-based effective treatment is a satisfying experience for doctors, but too many assume that patients will gratefully or accurately do what they are told, i.e. obtain the medicine and consume it as instructed. This assumption is wrong.

The rate of non-presentation (or redemption) of prescriptions in the UK is around 5%, but is up to 20% or even more in the elderly (who pay no prescription charge). Where lack of money to pay for the medicine is not the cause, this is due to lack of motivation.

Having obtained the medicine, some 25–50% (sometimes even more) of patients either fail to follow the instruction to a significant extent (taking 50–90% of the prescribed dose), or they do not take it at all. Patient non-compliance is identified as a major factor in therapeutic failure in both routine practice and in scientific therapeutic trials; but, sad to say, doctors are too often non-compliant about remedying this. All patients are potential non-compliers;\textsuperscript{56} clinical criteria cannot reliably predict good compliance, but non-compliance often can be predicted.

In addition to therapeutic failure, undetected non-compliance may lead to rejection of the best drug when it is effective, leading to substitution by second-rank medicines.

Non-compliance may occur because:

- the patient has not understood the instructions, so cannot comply,\textsuperscript{57} or
- understands the instructions, but fails to carry them out.

Prime factors for poor patient compliance are:

- **Frequency and complexity of the drug regimen.** Many studies attest to polypharmacy as an inhibitor of compliance, i.e. more than three


\textsuperscript{54}There is an agency for WHO publications in all UN countries.

\textsuperscript{55}The term compliance meets objection as having undertones of obsolete, authoritarian attitudes, implying ‘obedience’ to doctors’ ‘orders’. The words adherence or concordance are preferred by some, the latter because it expresses the duality of drug prescribing (by the doctor) and taking (by the patient), i.e. a therapeutic alliance. We retain compliance, pointing out that it applies equally to those doctors who neither keep up to date, nor follow prescribing instructions, and to patients who fail, for whatever reason, to keep to a drug regimen.

\textsuperscript{56}Even where the grave consequences of non-compliance are understood (glaucoma: blindness) (renal transplant: organ rejection), significant non-compliance has been reported in as many as 20% of patients; psychologists will be able to suggest explanations for this.

\textsuperscript{57}Cautionary tales:

- A 62-year-old man requiring a metered-dose inhaler (for the first time) was told to ‘spray the medicine to the throat’. He was found to have been conscientiously aiming and firing the aerosol to his anterior neck around the thyroid cartilage, four times a day for 2 weeks (Chiang A A, Lee J C 1994 New England Journal of Medicine 330:1690).
- A patient thought that ‘sublingual’ meant able to speak two languages; another that tablets cleared obstructed blood vessels by exploding inside them (E A Kay) – reference, no doubt, to colloquial use of the term ‘clot-busting drugs’ (for thrombolytics).
- These are extreme examples; most are more subtle and less detectable. Doctors may smile at the ignorant naivety of patients, but the smile should give way to a blush of shame at their own deficiencies as communicators.
drugs taken concurrently or more than three drug-taking occasions in the day (the ideal of one occasion only is often unattainable).

- **Unintentional non-compliance**, or forgetfulness,

  may be addressed by associating drug-taking with cues in daily life (breakfast, bedtime), by special packaging (e.g. calendar packs) and by enlisting the aid of others (e.g. carers, teachers).

- **‘Intelligent’ or wilful non-compliance**. Patients decide they do not need the drug (asymptomatic disease) or they do not like the drug (unwanted effects), or take 2–3-day ‘drug holidays’.

- **Illness**. This includes cognitive impairment and psychological problems, with depression being a particular problem.

- **Lack of information**. Oral instructions alone are not enough; one-third of patients are unable to recount instructions immediately on leaving the consulting room. Lucid and legible labelling of containers is essential, as well as patient-friendly information leaflets, which are increasingly available via doctors and pharmacists, and as package inserts.

- **Poor patient–doctor relationship and lack of motivation** to take medicines as instructed offer a major challenge to the prescriber whose diagnosis and prescription may be perfect, yet loses efficacy by patient non-compliance. Unpleasant disease symptoms, particularly

where these are recurrent and known by previous experience to be quickly relieved, provide the highest motivation (i.e. self-motivation) to comply. But particularly where the patient does not feel ill, adverse effects are immediate, and benefits are perceived to be remote, e.g. in hypertension, where they may be many years away in the future, doctors must consciously address themselves to motivating compliance. The best way to achieve compliance is to cultivate the patient–doctor relationship. Doctors cannot be expected actually to like all their patients, but it is a great help (where liking does not come naturally) if they make a positive effort to understand how individual patients must feel about their illnesses and their treatments, i.e. to empathise with their patients. This is not always easy, but its achievement is the action of the true professional, and indeed is part of their professional duty of care.

**Suggestions for doctors to enhance patient compliance**

- Form a non-judgemental alliance or partnership with the patient, giving the patient an opportunity to ask questions.

- Plan a regimen with the minimum number of drugs and drug-taking occasions, adjusted to fit the patient’s lifestyle. Use fixed-dose combinations, sustained-release (or injectable depot) formulations, or long $t_{[53]}$ drugs as appropriate; arrange direct observation of each dose in exceptional cases.

- Provide clear oral and written information adapted to the patient’s understanding and medical and cultural needs.

- Use patient-friendly packaging, e.g. calendar packs, where appropriate; or monitored-dose systems, e.g. boxes compartmented and labelled.

- See the patient regularly and not so infrequently that the patient feels the doctor has lost interest.

- Enlist the help of family members, carers, friends.

- Use computer-generated reminders for repeat prescriptions.

**Directly observed therapy** (DOT) (where a reliable person supervises each dose). In addition to the areas where supervision is obviously in the interest of patients, e.g. a child, DOT is employed (even

---

58Where non-compliance, whether intentional or unintentional, is medically serious it becomes necessary to bypass self-administration (unsupervised) and to resort to directly observed (supervised) oral administration or to injection (e.g. in schizophrenia).

59Of the many causes of failure of patient compliance, the following case must be unique: On a transatlantic flight the father of an asthmatic boy was seated in the row behind two doctors. He overheard one of the doctors expressing doubt about the long-term safety in children of inhaled corticosteroids. He interrupted the conversation, explaining that his son took this treatment; he had a lengthy conversation with one of the doctors, who gave his name. Consequently, on arrival, he faxed his wife at home to stop the treatment of their son immediately. She did so, and 2 days later the well controlled patient had a brisk relapse that responded to urgent treatment by the family doctor (who had been conscientiously following guidelines recently published in an authoritative journal). The family doctor later ascertained that the doctor in the plane was a member of the editorial team of the journal that had so recently published the guidelines that were favourable to inhaled corticosteroid (Cox S 1994 Is eavesdropping bad for your health? British Medical Journal 309:718).
imposed) among free-living uncooperative patients who may be a menace to the community, such as those with multiple drug-resistant tuberculosis.

A remarkable instance of non-compliance, with hoarding, was that of a 71-year-old man who attempted suicide and was found to have in his home 46 bottles containing 10 685 tablets. Analysis of his prescriptions showed that over a period of 17 months he had been expected to take 27 tablets of several different kinds daily.

From time to time there are campaigns to collect all unwanted drugs from homes in an area. Usually the public are asked to deliver the drugs to their local pharmacies. In one UK city (population 600 000), 500 000 ‘solid dose units’ (tablets, capsules, etc.) were handed in (see below, Opportunity cost); such quantities have even caused local problems for safe waste disposal.

Factors that are insignificant for compliance are: age\(^62\) (except at extremes), sex, intelligence (except at extreme deficiency) and educational level (probably).

**Over-compliance.** Patients (up to 20%) may take more drug than is prescribed, even increasing the dose by 50%. In diseases where precise compliance with frequent or complex regimens is important, for example in glaucoma where sight is at risk, there have been instances of obsessional patients responding to their doctors’ overemphatic instructions by clock-watching in a state of anxiety to avoid the slightest deviance from timed administration of the correct dose, to the extent that their daily (and nightly) life becomes dominated by this single purpose.

**Evaluation of patient compliance.** Merely asking patients whether they have taken the drug as directed is not likely to provide reliable evidence\(^63\). It is safest to assume that any event that can impair compliance, will sometimes happen.

Estimations of compliance come from a variety of measures. DOT (above) is the most accurate, and identification of the drug or metabolites in plasma (or an artificial biological marker in the case of a clinical trial) is persuasive at least of recent compliance.

Requiring patients to produce containers when they attend the doctor, who counts the tablets, seems to do little more than show the patient that the doctor cares about the matter (which is useful); a tablet absent from a container has not necessarily entered the patient’s body. On the other hand, although patients are known to practise deliberate deception, to maintain effective

---

\(^{62}\)After Drug and Therapeutics Bulletin 1981; 19:73. *Patient information leaflets. In economically privileged countries, original or patient-pack dispensing is becoming the norm, i.e. patients receive an unopened pack just as it left the manufacturer. The pack contains a Patient Information Leaflet (PIL) (which therefore accompanies each repeat prescription). Regulatory authorities increasingly determine its content. In this litigious age, requirements to be comprehensive and, to protect both manufacturer and regulatory authority, impair the patient-friendliness of PILs. But studies have shown that patients who receive leaflets are more satisfied than those who do not. Doctors need to have copies of these leaflets so that they can discuss with their patients what they are (or are not) reading.

\(^{63}\)But the elderly are commonly taking several drugs – a major factor in non-compliance – and monitoring compliance in this age group becomes particularly important. The over-sixties in the UK are, on average, each receiving two or three medications.

\(^{64}\)Hippocrates (460–377 BC) noted that patients are liars regarding compliance. The way the patient is questioned may be all important, e.g. ‘Were you able to take the tablets?’ may get a truthful reply, whereas ‘Did you take the tablets?’ may not, because the latter question may be understood by the patient as implying personal criticism (Pearson RM 1982 Who is taking their tablets? British Medical Journal 285:757).
deception successfully over long periods requires more effort than most patients are likely to make. Memory aids, such as drug diaries, monitored-dosage systems (e.g. compartmented boxes) and electronic containers that record times of opening are helpful.

Some pharmacodynamic effects, e.g. heart rate with a β-adrenoceptor blocker, provide a physiological marker as an indicator of the presence of drug in the body.

**Compliance in new drug development**

Non-compliance, discovered or undiscovered, can invalidate therapeutic trials (where compliance monitoring is essential). In new drug development trials the diluting effect of undetected non-compliance (prescribed doses are increased) can result in unduly high doses being initially recommended (licensed) (with toxicity in good compliers after marketing), so that the standard dose has soon to be urgently reduced (this has probably occurred with some new nonsteroidal anti-inflammatory drugs).

**DOCTOR COMPLIANCE**

Doctor compliance is the extent to which the behaviour of doctors fulfils their professional duty:

- not to be ignorant
- to adopt new advances when they are sufficiently proved (which doctors are often slow to do)
- to prescribe accurately
- to tell patients what they need to know
- to warn, i.e. to recognise the importance of the act of prescribing.

In one study in a university hospital, where standards might be expected to be high, there was an error of drug use (dose, frequency, route) in 3% of prescriptions and an error of prescription writing (in relation to standard hospital instructions) in 30%. Many errors were trivial, but many could have resulted in overdose, serious interaction or under-treatment.

In other hospital studies error rates in drug administration of 15–25% have been found, rates rising rapidly where four or more drugs are being given concurrently, as is often the case; studies of hospital inpatients show that each receives about six drugs, and up to 20 during a stay is not rare. Merely providing information (on antimicrobials) did not influence prescribing, but gently asking physicians to justify their prescriptions caused a marked fall in inappropriate prescribing.

On a harsher note, in recent years doctors who gave drugs, about which they later admitted ignorance (e.g. route of administration and/or dose), stood charged with manslaughter and were convicted. Shocked by this, fellow doctors have written to the medical press offering understanding sympathy to these, sometimes junior, colleagues: ‘There, but for the grace of God, go I’. But the public response is not sympathetic. Doctors put themselves forward as trained professionals who offer a service of responsible, competent provision of drugs that they have the legal right to prescribe. The public is increasingly inclined to hold them to that claim, and, where doctors seriously fail, to exact retribution.

If you do not know about a drug, find out before you act, or take the personal consequences, which, increasingly, may be very serious indeed.

**UNDERDOSING**

Use of suboptimal doses of drugs in serious disease occurs, sacrificing therapeutic efficacy to avoid serious adverse effects. Instances are commonest with drugs of low therapeutic index (see Index), i.e. where the effective and toxic dose ranges are close, or even overlap, e.g. heparin, anticancer drugs, aminoglycoside antimicrobials. In these cases dose adjustment

---

64 Accuracy includes legibility: a doctor wrote Intal (sodium cromoglycate) for an asthmatic patient; the pharmacist read it as Inderal (propranolol) – the patient died. See also, Names of drugs (Chapter 6).

65 Unlawful killing in circumstances that do not amount to murder (which requires an intention to kill), e.g. causing death by negligence that is much more serious than mere carelessness; reckless breach of the legal duty of care.

66 Attributed to John Bradford, an English preacher and martyr (16th century), on seeing a convicted criminal pass by.

67 A doctor wrote a prescription for isosorbide dinitrate 20 mg 6-hourly, but because of the illegibility of the handwriting the pharmacist dispensed felodipine in the same dose (maximum daily dose 10 mg). The patient died and a court ordered the doctor and pharmacist to pay compensation of $450,000 to the family. Charatan F 1999 Family compensated for death after illegible prescription. British Medical Journal 319:1456.
to obtain maximum benefit with minimum risk requires both knowledge and attentiveness.

THE CLINICAL IMPORTANCE OF MISSED DOSE(S)
Even the most conscientious of patients will miss a dose or doses occasionally. Patients should therefore be told whether this matters and what they should do about it, if anything.

Loss of therapeutic efficacy involves the pharmacokinetic properties of drugs. With some drugs of short $t_{1/2}$, the issue is simply a transient drop in plasma concentration below a defined therapeutic concentration. The issues are more complex where therapeutic effect may not decline in parallel with plasma concentration, as with recovery of negative feedback homoeostatic mechanisms (adrenocortical steroids).

A single missed dose may be important with some drugs, e.g. oral contraceptives, but with others (long $t_{1/2}$), omission of several doses is tolerated without any serious decline in efficacy, e.g. thyroxine (levothyroxine).

These pharmacokinetic considerations are complex and important, and are, or should be, taken into account by drug manufacturers in devising dosage schedules and informative data sheets. Manufacturers should aim at one or two doses per day (not more), and this is generally best achieved with drugs with relatively long biological effect $t_{1/2}$, or, where the biological effect $t_{1/2}$ is short, by using sustained-release formulations.

Discontinuation syndrome (recurrence of disease, rebound, or withdrawal syndrome) may occur due to a variety of mechanisms (see p. 000).

THE ECONOMISTS’ OBJECTIVE
The objective is to define needs, thereby enabling the deployment of resources according to priorities set by society, which has an interest in fairness between its members.

Resources can be distributed by the outcome of an unregulated power struggle between professionals and associations of patients and public pressure groups – all, no doubt, warm-hearted towards deserving cases of one kind or another, but none able to view the whole scene. Alternatively, distribution can occur by a planned evaluation that allows division of the resources based on some visible attempt at fairness.

A health economist writes:

Economics is the science of the distribution of wealth and resources. Prescribing doctors, who have a duty to the community as well as to individual patients, cannot escape involvement with economics.
The economist’s approach to evaluating drug therapies is to look at a group of patients with a particular disorder and the various drugs that could be used to treat them. The costs of the various treatments and some costs associated with their use (together with the costs of giving no treatment) are then considered in terms of impact on health status (survival and quality of life) and impact on other health care costs (e.g. admissions to hospital, need for other drugs, use of other procedures).

Economists are often portrayed as people who want to focus on cost, whereas in reality they see everything in terms of a balance between costs and benefits.

Four economic concepts have particular importance to the thinking of every doctor who takes up a pen to prescribe, i.e. to distribute resources:

- **Opportunity cost** means that which has to be sacrificed in order to carry out a certain course of action, i.e. costs are benefits foregone elsewhere. Money spent on prescribing is not available for another purpose; wasteful prescribing is an affront to those who are in serious need, e.g. institutionalised mentally handicapped citizens who everywhere would benefit from increased resources.

- **Cost–effectiveness analysis** is concerned with how to attain a given objective at minimal financial cost, e.g. prevention of post-surgical venous thromboembolism by heparins, warfarin, aspirin, external pneumatic compression. Analysis includes the cost of materials, adverse effects, any tests, nursing and doctor time, duration of stay in hospital (which may greatly exceed the cost of the drug).

- **Cost–benefit analysis** is concerned with issues of whether (and to what extent) to pursue objectives and policies; it is thus a broader activity than cost–effectiveness analysis and puts monetary values on the quality as well as on the quantity (duration) of life.

- **Cost–utility analysis** is concerned with comparisons between programmes, such as an antenatal drug treatment, which saves a young life, or a hip replacement operation, which improves mobility in a man of 60 years. Such differing issues are also the basis for comparison by computing quality-adjusted life-years (see below).

An allied measure is the **cost–minimisation analysis**, which finds the least costly programme among those shown or assumed to be of equal benefit. Economic analysis requires that both quantity and quality of life be measured. The former is easy, the latter is hard to determine.

In the UK the National Institute for Health and Clinical Excellence (NICE) appraises the clinical effectiveness and cost effectiveness of drugs, devices and diagnostic tools, and advises health-care professionals in the NHS on their use. The NHS is legally obliged to make resources available to implement NICE guidance, so avoiding differential treatment according to a patient’s area of residence – so-called ‘postcode prescribing’.

**QUALITY OF LIFE**

Everyone is familiar with the measurement of the benefit of treatment in saving or extending life, i.e. life expectancy: the measure is the quantity of life (in years). But it is evident that life may be extended and yet have a low quality, even to the point that it is not worth having at all. It is therefore useful to have a unit of health measurement that combines the quantity of life with its quality, to place individual and social decision-making on a sounder basis than mere intuition. Economists met this need by developing the **quality-adjusted life-year** (QALY) whereby estimations of years of life expectancy are modified according to estimations of quality of life.

Quality of life has four principal dimensions:

1. Physical mobility
2. Freedom from pain and distress
3. Capacity for self-care
4. Ability to engage in normal work and social interactions.

The approach for determining quality of life is by questionnaire, to measure what the subject perceives as personal health. The assessments are refined to provide improved assessment of the benefits and risks of medicines to the individual and to society. The challenge is to ensure that these are sufficiently robust to make resource allocation decisions between, for example, the rich and the poor, the educated and the uneducated, the old and the young, as well as between groups of patients with very different diseases. Plainly, quality of life is a major aspect of what is called outcomes research.

---

SELF-MEDICATION

To feel unwell is common, although the frequency varies with social and cultural circumstances. People commonly experience symptoms or complaints, and commonly want to take remedial action. In one study of adults randomly selected from a large population, 9 out of 10 had one or more complaints in the 2 weeks before interview; in another of pre-menopausal women, a symptom occurred as often as 1 day in 3; in both studies a medicine was taken for more than half of these occurrences.

SELF-MEDICATION AND CONSUMER RIGHTS

Increasingly, educated and confident consumers are aware of five consumer rights (United Nations charter):

- access (to a wide range of products)
- choice (self-determination)
- information (on which to base choice)
- redress (when things go wrong)
- safety (appropriate to the use of the product).

Modern consumers (patients) wish to take a greater role in the maintenance of their own health and are often competent to manage (uncomplicated) chronic and recurrent illnesses (not merely short-term symptoms) after proper medical diagnosis and with only occasional professional advice, e.g. use of histamine H₂-receptor blockers, topical corticosteroids and antifungals, and oral contraceptives. They are understandably unwilling to submit to the inconvenience of visiting a doctor for what they rightly feel they can manage for themselves, given adequate information. Legislation in the USA permits the advertising of prescription drugs direct to consumer (DTC). Advertising has spurred millions of people to take cyclo-oxygenase-2 (COX-2) inhibitors, even when not indicated (see rofecoxib, p. 000).

Increased consumer autonomy leads to satisfied:

- consumers (above)
- governments (lower drug bill)
- industry (profits)
- doctors (reduced workload).

The pharmaceutical industry enthusiastically estimates that extending the use of self-medication to all potentially self-treatable illnesses could save 100 to 150 million general practitioner consultations per year in the UK (population 60 million). But there will also be added costs as pharmacists extend their responsibilities for supply and information.

Regulatory authorities are increasingly receptive to switching hitherto prescription-only medicines (POM) for self-medication (over-the-counter, OTC sale) via pharmacies (P) or via any retail outlet (general sale). The operation is known as POM-OTC or POM-P ‘switch’. It requires particularly exacting standards of safety.

Self-medication is appropriate for:

- short-term relief of symptoms where accurate diagnosis is unnecessary
- uncomplicated cases of some chronic and recurrent disease (a medical diagnosis having been made and advice given).

Safety in self-medication (an overriding requirement) depends on four items:

1. The drug – its inherent properties, dose and duration of use, including its power to induce dependence
2. The formulation – devised with unsupervised use in mind, e.g. low dose
3. Information – available with all purchases (printed) and rigorously reviewed (by panels of potential users) for user-friendliness and adequacy for a wide range of education and intellectual capacity
4. Patient compliance.

Doctors must recognise the increasing importance of questioning about self-medication when taking a drug history (see p. 000).

GUIDE TO FURTHER READING


The whole issue (18 March 2000) should be consulted for its extensive coverage of the subject of medical error

Prescriptions of pure drugs or of formulations from the British National Formulary (BNF) are satisfactory for almost all purposes. The composition of many of the preparations in the BNF is laid down in official pharmacopoeias, e.g. British Pharmacopoeia (BP). There are also many national and international pharmacopoeias.

Traditional extemporaneous prescription-writing art, defining drug, base, adjuvant, corrective, flavouring and vehicle, is obsolete, as is the use of the Latin language. Certain convenient Latin abbreviations do survive for lack of convenient English substitutes. They appear below, without approval or disapproval.

The elementary requirements of a prescription are that it should state what is to be given to whom and by whom prescribed, and give instructions on how much should be taken, how often, by what route and for how long, or the total quantity to be supplied, as below.

1. **Date.**
2. **Address of doctor.**
3. **Name and address of patient:** date of birth is also desirable for safety reasons; in the UK it is a legal requirement for children aged under 12 years.
4. **R** – This is a traditional esoteric symbol for the word 'Recipe' – 'take thou', which is addressed to the pharmacist. It is pointless; but as many doctors gain a harmless pleasure from writing it with a flourish before the name of a proprietary preparation of whose exact nature they may be ignorant, it is likely to survive as a sentimental link with the past.
5. **Name and dose of the medicine.**

*Abbreviations.* Only abbreviate where there is an official abbreviation. Never use unofficial abbreviations or invent your own; it is not safe to do so.

**Quantities (after BNF):**
- 1 gram or more: write 1 g, etc.
- less than 1 g: write as milligrams: 500 mg, not 0.5 g
- less than 1 mg: write as micrograms, e.g. 100 micrograms, not 0.1 mg

---

**APPENDIX: THE PRESCRIPTION**

The prescription is the means by which patients receive medicines that are considered unsafe for sale directly to the public. Its format is officially regulated to ensure precision in the interests of safety and efficacy, and to prevent fraudulent misuse; full details appear in national formularies, and prescribers have a responsibility to comply with these.

---

Mason S, Tovey P, Long A F 2002 Evaluating complementary and alternative medicine (CAM) and the human effect. Clinical Medicine 5:(4):361–367
Meltzer M I 2001 Introduction to health economics for physicians. Lancet 358:993–998 (and subsequent papers in this quintet)

---

**APPENDIX: THE PRESCRIPTION**

The prescription is the means by which patients receive medicines that are considered unsafe for sale directly to the public. Its format is officially regulated to ensure precision in the interests of safety and efficacy, and to prevent fraudulent misuse; full details appear in national formularies, and prescribers have a responsibility to comply with these.
TOPICS IN DRUG THERAPY

- for decimals, a zero should precede the decimal point where there is no other figure, e.g. 0.5 mL, not .5 mL; for a range, 0.5–1 g
- do not abbreviate microgram, nanogram or unit
- use millilitre (ml or mL), not cubic centimetre (cc)
- for home/domestic measures, see below.

State dose and dose frequency; for ‘as required’, specify minimum dose interval or maximum dose per day.

6. Directions to the pharmacist, if any: ‘mix’, ‘make a solution’. Write the total quantity to be dispensed (if this is not stated in 5 above); or duration of supply.

7. Instruction for the patient, to be written on container by the pharmacist. Here brevity, clarity and accuracy are especially important. It is dangerous to rely on the patient remembering oral instructions. The BNF provides a list of recommended ‘cautionary and advisory labels for dispensed medicines’, representing a balance between ‘the unintelligibly short and the inconveniently long’, for example: ‘Do not stop taking this medicine except on your doctor’s advice’.

Pharmacists nowadays use their own initiative in giving advice to patients.

8. Signature of doctor.

Example of a prescription for a patient with an annoying unproductive cough:

1, 2, 3, as above
4. R
5. Codeine Linctus, BNF, 5 ml
6. Send 60 ml
7. Label: Codeine Linctus (or NP). Take 5 ml twice a day and on retiring
8. Signature of doctor.

Computer-issued prescriptions must conform to recommendations of professional bodies. Computer-generated facsimile signatures do not meet the legal requirement.

If altered by hand (undesirable), the alteration must be signed.

Medicine containers. Reclosable child-resistant containers and blister packs are now standard, as is dispensing in manufacturers’ original sealed packs containing a patient information leaflet. These add to immediate cost but may save money in the end (increased efficiency of use, and safety).

Unwanted medicines. Patients should be encouraged to return these to the original supplier for disposal.

Drugs liable to cause dependence or be the subject of misuse. Doctors have a particular responsibility to ensure that: (1) they do not create dependence, (2) the patient does not increase the dose and create dependence, (3) they do not become an unwitting source of supply to addicts. To many such drugs, special prescribing regulations apply (see BNF).

Abbreviations (see also Weights and measures, below)

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>b.d.:</td>
<td>twice a day (b.i.d. is also used)</td>
</tr>
<tr>
<td>BNF</td>
<td>British National Formulary</td>
</tr>
<tr>
<td>BP</td>
<td>British Pharmacopoeia</td>
</tr>
<tr>
<td>BPC</td>
<td>British Pharmaceutical Codex</td>
</tr>
<tr>
<td>i.m.:</td>
<td>by intramuscular injection</td>
</tr>
<tr>
<td>IU</td>
<td>International Unit</td>
</tr>
<tr>
<td>i.v.:</td>
<td>by intravenous injection</td>
</tr>
<tr>
<td>NP:</td>
<td>nomen proprium (proper name)</td>
</tr>
<tr>
<td>o.d.:</td>
<td>every day</td>
</tr>
<tr>
<td>o.m.:</td>
<td>every morning</td>
</tr>
<tr>
<td>o.n.:</td>
<td>every night</td>
</tr>
<tr>
<td>p.o.:</td>
<td>by mouth</td>
</tr>
<tr>
<td>p.r.:</td>
<td>by the anal/rectal route as required. It is best to add the maximum frequency of repetition, e.g. aspirin and codeine tablets, 1 or 2 p.r.n., 4-hourly</td>
</tr>
<tr>
<td>p.r.n.:</td>
<td>pro re nata</td>
</tr>
<tr>
<td>p.v.:</td>
<td>by the vaginal route four times a day (q.i.d. is also used)</td>
</tr>
<tr>
<td>q.d.s.:</td>
<td>quater die sumendus</td>
</tr>
<tr>
<td>rep:</td>
<td>repetatur</td>
</tr>
<tr>
<td>q.i.d.:</td>
<td>let it be repeated, as in rep. mist(ura), repeat the mixture</td>
</tr>
<tr>
<td>s.c.:</td>
<td>by subcutaneous injection immediately</td>
</tr>
<tr>
<td>stat:</td>
<td>statim</td>
</tr>
<tr>
<td>t.d.s.:</td>
<td>ter (in) die sumendus</td>
</tr>
<tr>
<td>t.i.d.:</td>
<td>three times a day (t.i.d. is also used)</td>
</tr>
</tbody>
</table>
WEIGHTS AND MEASURES

In this book doses are given in the metric system, or in international units (IU) when metric doses are impracticable.

Equivalents:
1 litre (l or L) = 1.76 pints
1 kilogram (kg) = 2.2 pounds (lbs).

Abbreviations:
1 gram (g)
1 milligram (mg) ($1 \times 10^{-3}$ g)
1 microgram ($1 \times 10^{-6}$ g)
1 nanogram ($1 \times 10^{-9}$ g)
1 decilitre (dL) ($1 \times 10^{-1}$ L)
1 millilitre (mL) ($1 \times 10^{-3}$ L).

Home/domestic measures. A standard 5-ml spoon and a graduated oral syringe are available. Otherwise the following approximations will serve:

- 1 tablespoonful = 14 ml (or mL)
- 1 dessertspoonful = 7 ml (or mL)
- 1 teaspoonful = 5 ml (or mL).

PERCENTAGES, PROPORTIONS, WEIGHT IN VOLUME

Some solutions of drugs (e.g. local anaesthetics, epinephrine/adrenaline) for parenteral use are labelled in a variety of ways: percentage, proportion, or weight in volume (e.g. 0.1%, 1 : 1000, 1 mg per mL). In addition, dilutions may have to be made by doctors at the time of use. Such drugs are commonly dangerous in overdose and great precision is required, especially as any errors are liable to be by a factor of 10 and can be fatal. Doctors who do not feel confident with such calculations (because they do not do them frequently) should feel no embarrassment, but should recognise that they have a responsibility to check their results with a competent colleague or pharmacist before proceeding.

---

73 Spell out in full in prescriptions.
74 Called to an emergency tension pneumothorax on an intercontinental flight, two surgeons, who chanced to be passengers, were provided with lidocaine 100 mg in 10 mL (in the aircraft medical kit). They were accustomed to thinking in percentages for this drug and ‘in the heat of the moment’ neither was able to make the conversion. Chest surgery was conducted successfully with an adapted wire coat-hanger as a trocar (‘sterilised’ in brandy), using a urinary catheter. The patient survived the flight and recovered in hospital. Wallace WA 1995 Managing in-flight emergencies: a personal account. British Medical Journal 311:374.
# Author Query Form

**Book:**

**Chapter No.: 2**

<table>
<thead>
<tr>
<th>Query</th>
<th>Details Required</th>
<th>Author's Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>[AU1]</td>
<td>Cross-reference to be added at proof stage.</td>
<td></td>
</tr>
<tr>
<td>[AU2]</td>
<td>Cross-reference to be added at proof stage.</td>
<td></td>
</tr>
<tr>
<td>[AU3]</td>
<td>Cross-reference to be added at proof stage.</td>
<td></td>
</tr>
<tr>
<td>[AU4]</td>
<td>Cross-reference to be added at proof stage.</td>
<td></td>
</tr>
<tr>
<td>[AU5]</td>
<td>Cross-reference to be added at proof stage.</td>
<td></td>
</tr>
<tr>
<td>[AU6]</td>
<td>Cross-reference to be added at proof stage.</td>
<td></td>
</tr>
<tr>
<td>[AU7]</td>
<td>Cross-reference to be added at proof stage.</td>
<td></td>
</tr>
<tr>
<td>[AU8]</td>
<td>Cross-reference to be added at proof stage.</td>
<td></td>
</tr>
<tr>
<td>[AU9]</td>
<td>Cross-reference to be added at proof stage.</td>
<td></td>
</tr>
<tr>
<td>[AU10]</td>
<td>Cross-reference to be added at proof stage.</td>
<td></td>
</tr>
<tr>
<td>[AU11]</td>
<td>Cross-reference to be added at proof stage.</td>
<td></td>
</tr>
</tbody>
</table>
Discovery and development of drugs

SYNOPSIS
- Preclinical drug development. Discovery of new drugs in the laboratory is an exercise in prediction.
- Techniques of discovery. Sophisticated molecular modelling allows precise design of potential new therapeutic substances and new technologies have increased the rate of development of potential medicines.
- Studies in animals.
- Ethical issues.
- Need for animal testing.
- Prediction. Failures of prediction occur and a drug may be abandoned at any stage, including after marketing. New drug development is a colossally expensive and commercially driven activity.
- Orphan drugs and diseases.

PRECLINICAL DRUG DEVELOPMENT

The development of new medicines (drugs) is an exercise in extrapolation from laboratory studies in vitro and in vivo (animals), in order to predict what the agent will do in humans. Medicinal therapeutics rests on the two great supporting pillars of pharmacology:

- Selectivity— the desired effect alone is obtained: ‘We must learn to aim, learn to aim with chemical substances’ (Paul Ehrlich).
- Dose— ‘... The dose alone decides that something is no poison’ (Paracelsus).

For decades, the rational discovery of new medicines has depended on modifications of the molecular structures of increasing numbers of known natural chemical mediators. Often the exact molecular basis of drug action is unknown, and this book contains frequent examples of old drugs whose mechanism of action remains mysterious. The evolution of molecular medicine (including recombinant DNA technology) in the past 30 years has led to a new pathway of drug discovery: pharmacogenomics. This broad term encompasses all genes in the genome that may determine drug response, desired and undesired. Completion of the Human Genome Project in 2001 yielded a minimum of 30,000 potential drug targets, although the function of many of these genes remains unknown. In the future, drugs may be designed according to individual genotypes, thereby enhancing safety as well as efficacy.

The chances of discovering a truly novel medicine, i.e. one that does something valuable that had previously not been possible (or that does safely what could previously have been achieved only with substantial risk), are increased when the development programme is founded on precise knowledge, at molecular level, of the biological processes it is desired to change. The commercial rewards of a successful product are potentially enormous and

1 Paul Ehrlich (1845–1915), a German scientist, pioneered the scientific approach to drug discovery. The 606th organic arsenical that he tested against spirochaetes (in animals) became a successful medicine (Salvarsan 1910); it and a minor variant were used against syphilis until superseded by penicillin in 1945.

2 Paracelsus (1493–1541) was a controversial figure who has been portrayed as both ignorant and superstitious. He had no medical degree; he burned the classical medical works (Galen, Avicenna) before his lectures in Basle (Switzerland) and had to leave the city following a dispute about fees with a prominent churchman. He died in Salzburg (Austria), either as a result of a drunken debauch or because he was thrown down a steep incline by ‘hitmen’ employed by jealous local physicians. But he was right about the dose.

3 An example of the opportunity created by pharmacogenomics comes in the announcement by a major pharmaceutical company of plans to search the entire human genome for genetic evidence of intolerance to one of its drugs. If achieved, adverse reactions to the drug would be virtually eliminated.
provide a massive incentive for developers to invest and risk huge sums of money.

Studies of signal transduction, the fundamental process by which cells talk to one another as intracellular proteins transmit signals from the surface of the cell to the nucleus inside, have opened an entirely new approach to the development of therapeutic agents that can target discrete steps in the body’s elaborate pathways of chemical reactions. The opportunities are endless.\(^4\)

The molecular approach to drug discovery should enable a ‘molecular dissection’ of any disease process. There are two immediate consequences:

- More potential drugs and therapeutic targets will be produced than can be experimentally validated in animals and humans. A further risk is that this ‘production line’ approach could lead to a loss of integration of the established specialities (chemistry, biochemistry, pharmacology) and to an overall lack of understanding of how physiological and pathophysiological processes contribute to the interaction of drug and disease.
- New drugs could be targeted at selected groups of patients based on their genetic make-up. This concept of ‘the right medicine for the right patient’ is the basis of pharmacogenetics (see p. 000), the genetically determined variability in drug response.

Pharmacogenetics has gained momentum from recent advances in molecular genetics and genome sequencing, due to:

- Rapid screening for specific gene polymorphisms (see p. 000)
- Knowledge of the genetic sequences of target genes such as those coding for enzymes, ion channels, and other receptor types involved in drug response

There are high expectations of pharmacogenetics and its progeny, pharmacoproteomics (understanding of and drug effects on protein variants). They include:

- The identification of subgroups of patients with a disease or syndrome based on their genotype
- Targeting of specific drugs for patients with specific gene variants

Consequences of these expectations include: smaller clinical trial programmes, better understanding of the pharmacokinetics and dynamics according to genetic variation, and simplified monitoring of adverse events after marketing.

*New drug development* proceeds thus:

- Idea or hypothesis
- Design and synthesis of substances
- Studies on tissues and whole animal (preclinical studies)
- Studies in humans (clinical studies) (see Chapter 4)
- Granting of an official licence to make therapeutic claims and to sell (see Chapter 5)
- Post-licensing (marketing) studies of safety and comparisons with other medicines.

The (critical) phase of progress from the laboratory to humans is termed *translational science*. It was defined as ‘the application of biomedical research (pre-clinical and clinical), conducted to support drug development, which aids in the identification of the appropriate patient for treatment (patient selection), the correct dose and schedule to be tested in the clinic (dosing regimen) and the best disease in which to test a potential agent’.\(^5\)

It will be obvious from the account that follows that drug development is an extremely arduous, highly technical and enormously expensive operation. Successful developments (1% of compounds that proceed to full test eventually become licensed medicines) must carry the cost of the failures (99%).\(^6\)

---


\(^6\) The cost of development of a new chemical entity (NCE) (a novel molecule not previously tested in humans) from synthesis to market (general clinical use) is estimated at US$500 million; the process may take as long as 15 years (including up to 10 years for clinical studies), which is relevant to duration of patent life and so to ultimate profitability; if the developer does not see profit at the end of the process, the investment will not be made. The drug may fail at any stage, including the ultimate, i.e. at the official regulatory body after all the development costs have been incurred. It may also fail (due to adverse effects) within the first year after marketing, which constitutes a catastrophe (in reputation and finance) for the developer as well as for some of the patients. Pirated copies of full regulatory dossiers have substantial black market value to competitor companies, who have used them to leapfrog the original developer to obtain a licence for their unresearched copied molecule. Dossiers may be enormous, even one million pages or the electronic equivalent, the latter being very convenient as it allows instant searching.
It is also obvious that such programmes are likely to be carried to completion only when the organisations and the individuals within them are motivated overall by the challenge to succeed and to serve society, as well as to make money. A professor of clinical pharmacology writes:

Let us get one thing straight: the drug industry works within a system that demands it makes a profit to satisfy shareholders. Indeed, it has a fiduciary duty to do so. The best way to make a lot of money is to invent a drug that produces a dramatically beneficial clinical effect, is far more effective than existing options, and has few unwanted effects. Unfortunately most drugs fall short of this ideal.⑧

**TECHNIQUES OF DISCOVERY**

(See Figure 3.1)

The newer technologies, the impact of which has yet to be fully felt, include the following.

**Molecular modelling** aided by three-dimensional computer graphics (including virtual reality) allows the design of structures based on new and known molecules to enhance their desired, and to eliminate their undesired, properties to create highly selective targeted compounds. In principle all molecular structures capable of binding to a single high-affinity site can be modelled.

**Combinatorial chemistry** involves the random mixing and matching of large numbers of chemical building blocks (amino acids, nucleotides, simple chemicals) to produce ‘libraries’ of all possible combinations. This technology can generate billions of new compounds that are initially

---

⑦ Held or given in trust (OED).

evaluated using automated robotic high-throughput screening devices that can handle thousands of compounds a day. If the screen records a positive response, the compound is further investigated using traditional laboratory methods, and the molecule is manipulated to enhance selectivity and/or potency (above).

Proteins as medicines: biotechnology. The targets of most drugs are proteins (cell receptors, enzymes) and it is only lack of technology that has hitherto prevented the exploitation of proteins (and peptides) as medicines. This technology is now available, although there are practical problems in getting the proteins to the target site in the body (they are digested when swallowed and cross cell membranes with difficulty). Biotechnology involves the use of recombinant DNA technology/genetic engineering to clone and express human genes, for example in microbial (Escherichia coli or yeast) cells so that they manufacture proteins that medicinal chemists have not been able to synthesise. Such techniques can deliver hormones and autacoids in commercial amounts (such as insulin and growth hormone, erythropoietins, cell growth factors and plasminogen activators, interferons, vaccines and immune antibodies).

Transgenic animals (that breed true for the gene) are also being developed as models for human disease as well as for production of medicines.

The polymerase chain reaction (PCR) is a method of gene amplification that does not require living cells; it takes place in vitro and can produce (in a cost-effective way) commercial quantities of pure potential medicines.

Genetic medicines. Synthetic oligonucleotides are being developed to target sites on DNA sequences or genes (double-stranded DNA: triplex approach) or messenger RNA (the antisense approach), so that the production of disease-related proteins is blocked. These oligonucleotides offer prospects of treatment for cancers and viruses without harming healthy tissues.10,11

Gene therapy of human genetic disorders is a strategy in which nucleic acid, usually in the form of DNA, is administered to modify the genetic repertoire for therapeutic purposes, e.g. cystic fibrosis. ‘The era of the gene as drug’ is clearly upon us (R G Crystal). Significant problems remain; in particular the methods of delivery. Three methods are available: an injection of ‘naked’ DNA; using a virus as carrier with DNA incorporated into its genome; or DNA encapsulated within a liposome.

Immunopharmacology Understanding of the molecular basis of immune responses has allowed the definition of mechanisms by which cellular function is altered by a legion of local hormones or autacoids in, for example, infections, cancer, autoimmune diseases, organ transplant rejection. These processes present targets for therapeutic intervention – hence the rise of immunopharmacology.

Positron emission tomography (PET) allows non-invasive pharmacokinetic and pharmacodynamic measurements in previously inaccessible sites, e.g. the brain in intact humans and animals.

Older approaches to discovery of new medicines that continue in use include:

- Animal models of human disease or an aspect of it of varying relevance to humans.
- Natural products: modern technology for screening has revived interest and intensified the search. Multinational pharmaceutical companies now scour the world for leads from microorganisms (in soil or sewage or even from insects entombed in amber 40 million years ago), fungi, plants and animals. Developing countries in the tropics (with their luxuriant natural resources) are prominent targets in this search and have justly complained of

---

9 It is too early to say what success these programmes may have but automation of assays, possibly coupled to similar automation of syntheses, promises to speed up the search for new leads which is the rate-limiting step in the introduction of really novel therapeutic agents. Their value in medicine will depend upon the significance of the control mechanism concerned in the pathogenesis of a disease process. Critics fear that the result may well be large numbers of drugs in search of a disease to treat (Dollery C T 1994 Harveian Oration: Medicine and the pharmacological revolution. Journal of the Royal College of Physicians of London 28:59–69).

exploitation (‘gene robbery’). Many now require formal profit-sharing agreements to allow such searches.

- Traditional medicine, which is being studied for possible leads to usefully active compounds.
- Modifications of the structures of known drugs: these are obviously likely to produce more agents with similar basic properties, but may deliver worthwhile improvements. It is in this area that the ‘me too’ and ‘me again’ drugs are developed (sometimes for purely commercial reasons).
- Random screening of synthesised and natural products.
- New uses for drugs already in general use as a result of intelligent observation and serendipity, or advancing knowledge of molecular mechanisms, e.g. aspirin for antithrombotic effect.

**DRUG QUALITY**

It is easy for an investigator or prescriber, interested in pharmacology, toxicology and therapeutics, to forget the fundamental importance of chemical and pharmaceutical aspects. An impure, unstable drug or formulation is useless. Pure drugs that remain pure drugs after 5 years of storage in hot, damp climates are vital to therapeutics. The record of manufacturers in providing this is impressive.

**STUDIES IN ANIMALS**

Generally, the following are undertaken:

- **Pharmacodynamics** – to investigate the actions relating to the proposed therapeutic use. In addition, there is a need to investigate potential undesirable pharmacodynamic effects of the substance on physiological functions.

- **Pharmacokinetics** – to study of the fate of the active substance and its metabolites, within the organism (absorption, distribution, metabolism and excretion of these substances). The programme should be designed to allow comparison and extrapolation between animal and human.

- **Toxicology** – to reveal physiological and/or histopathological changes induced by the drug, and to determine how these changes relate to dose. These involve:
  - Acute toxicity: single-dose studies that allow qualitative and quantitative assessment of toxic reactions
  - Chronic and subchronic toxicity: repeat-dose studies to characterise the toxicological profile of a drug following repeated administration. This includes the identification of potential target organs and exposure–response relationships, and may include the potential for reversibility of effects.

  Generally, it is desirable that tests be performed in two relevant species, based on the pharmacokinetic profile, one a rodent and one a non-rodent. The duration of the studies depends on the conditions of clinical use and is defined by Regulatory Agencies (Tables 3.1 & 3.2).

- **Genotoxicity** – to reveal the changes that a drug may cause in the genetic material of individuals or cells. Mutagenic substances present a hazard to health because exposure carries the risk of inducing germline mutation (with the possibility of inherited disorders) and somatic mutations (including those leading to cancer). A standard battery of investigations includes: a test for gene mutation in bacteria (e.g. the Ames test); an in vitro test with cytogenetic

---

12 Serendipity is the faculty of making fortunate discoveries by general sagacity or by accident; the word derives from a fairytale about three princes of Serendip (Sri Lanka) who had this happy faculty.

13 Mouse, rat, hamster, guinea-pig, rabbit, cat, dog, monkey are used (but not all for any one drug). Non-clinical (pharmacotoxicological) studies must be carried out in conformity with the provisions of internationally agreed standards known as Good Laboratory Practice (GLP). In Europe, regulations ensure that all tests on animals are conducted in accordance with Council Directive 86/609/EEC. Studies in animals can be substituted by validated in vitro tests provided that the test results are of comparable quality and usefulness for the purpose of safety evaluation. The pharmacological and toxicological tests must demonstrate the potential toxicity of the product and any dangerous or undesirable toxic effects that may occur under the proposed conditions of use in human beings; these should be evaluated in relation to the pathological condition concerned. The studies must also demonstrate the pharmacological properties of the product, in both qualitative and quantitative relationship to the proposed use in human beings.

14 Details can be found at: http://www.emea.eu.int.
evaluation of chromosomal damage with mammalian cells or an in vitro mouse lymphoma thymidine kinase (tk) assay; an in vivo test for chromosomal damage using rodent haematopoietic cells (e.g. the mouse micronucleus test).

Carcinogenicity to reveal carcinogenic effects. These studies are performed for any medicinal product if its expected clinical use is prolonged (about 6 months), either continuously or repeatedly. These studies are also recommended if there is concern about their carcinogenic potential, e.g. from a product of the same class or similar structure, or from evidence in repeated-dose toxicity studies. Studies with unequivocally genotoxic compounds are not needed, as they are presumed to be trans-species carcinogens, implying a hazard to humans.

Reproductive and developmental toxicity these tests study effects on adult male or female reproductive function, toxic and teratogenic effects at all stages of development from conception to sexual maturity and latent effects, when the medicinal product under investigation has been administered to the female during pregnancy. Embryo/fetal toxicity studies are normally conducted on two mammalian species, one a non-rodent. If the metabolism of a drug in particular species is known to be similar to that in humans, it is usual to include this species. Studies in juvenile animals may also be required prior to developing drugs for use in children.

Local tolerance to ascertain whether drugs are tolerated at sites in the body at which they may come into contact in clinical use. The testing strategy is such that any mechanical effects of administration or purely physicochemical actions of the product can be distinguished from toxicological or pharmacodynamic ones.

Biotechnology-derived pharmaceuticals present a special case and the standard regimen of toxicology studies is not appropriate. The choice of species used depends on the expression of the relevant receptor. If no suitable species exists, homologous proteins or transgenic animals expressing the human receptor may be studied and additional immunological studies are required.

ETHICS AND LEGISLATION

Controversy surrounding the use of animals in scientific research is not new. The renowned Islamic physician Avicenna (980–1037) was aware of the issues for he held that ‘the experimentation must be done with the human body, for testing a drug on a lion or a horse might not prove anything about its effect on man’. Leonardo da Vinci (1452–1519)

DISCOVERY AND DEVELOPMENT OF DRUGS

predicted that one day experimentation on animals would be judged a crime, but Descartes\(^ 1\) asserted that 'Animals do not speak, therefore they do not think, therefore they do not feel.' Later, Jeremy Bentham (1748–1832), the founding father of utilitarian philosophy, asked of animals: 'The question is not, Can they reason? nor Can they talk? but Can they suffer?'.

In our present world, billions of animals are raised to provide food and many to be used for scientific experiments. The arguments that evolve from this activity centre on the extent to which non-human animals can be respected as sentient beings of moral worth, albeit with differences between species. In recent years, a boisterous animal rights movement, asserting the moral status of animals, has challenged their use as experimental subjects.\(^ 1\) Mainstream medical and scientific opinion around the world accepts that animal research continues to be justified, subject to important protections. This position is based on the insight that research involving animals has contributed hugely to advances in biological knowledge that have in turn allowed modern therapeutics to improve human morbidity and mortality. Animal models contribute enormously to the understanding of human physiological and disease because we share so many biological characteristics. A medicine when introduced into the organism is exposed to a vast array of conditions that we do not fully understand and are unable to reproduce outside the living body. The study of a drug in the whole organism gives more information, more rapidly.

Safety testing in animals is at present the only reliable way to evaluate risks before undertaking clinical trials of potentially useful medicines in humans. The investigation of reproductive effects and potential carcinogenicity would not be undertaken in humans for both ethical and practical reasons. Animal testing eliminates many unsafe test materials before clinical testing on humans, and minimises the risk of possible adverse effects when people are exposed to potential new medicines. In other words, experiments in animal models provide a critical safety check on candidate drugs; potentially hazardous or ineffective drugs can be eliminated and for those drugs that do progress to clinical trials, target organs identified in animal studies can be monitored.

Animal research has contributed to virtually every area of medical research, and almost all of the best known drug and surgical treatments of the past and present owe their origins in some way to evidence from animals. The antibacterial effectiveness of penicillin was as proved in tests on mice. Insulin came about because of research on rabbits and dogs in the 1920s. Poliomyelitis epidemics, which until the 1950s killed and paralysed millions of children, were consigned to history by vaccines resulting from studies on a range of laboratory animals, including monkeys. Major heart surgery, such as coronary artery bypass grafts and heart transplants, was developed through research on dogs and pigs. The BCG vaccine for tuberculosis was developed through research on rats and mice. Meningitis due to *Haemophilus influenzae* type b, formerly common especially in children, is now almost unknown in the UK because of a vaccine developed through work on mice and rabbits. Almost all of the highly effective drug treatments we currently use were developed using animals: \(\beta\)-adrenoceptor blockers, angiotensin-converting enzyme inhibitors, cytotoxics, analgesics, psychotropics, and so on.

Given this evidence, there is broad public support for the position that experiments on animals is a regrettable necessity that should be limited to what is deemed essential while alternatives are developed. In the UK, for example, this reservation is expressed in progressively more stringent legislation. The Animals (Scientific Procedures) Act 1986 makes it an offence to carry out any scientific procedure on animals except under licence, the requirements of which include that:

- Animals are only used as a last resort.
- Every practical step is taken to avoid distress or suffering.
- The smallest possible number of animals is used.
- The potential benefits have to be weighed against the cost to the animals; the simplest or least sentient species is used.
- The work is realistic and achievable, and the programme designed in the way most likely to produce satisfactory results.

\(^{1}\) René Descartes (1596–1650), French philosopher, mathematician and scientist, acknowledged as one of the chief architects of the modern age.

\(^{1\text{st}}\) The publication of *Animal Liberation* (New York: New York Review/Randome House) by Peter Singer in 1975 is widely regarded as having provided its moral foundation.
PREDICTION

It is frequently pointed out that regulatory guidelines are not rigid requirements to be universally applied. But whatever the intention, they do tend to be treated as minimum requirements, if only because research directors fear to risk holding up their expensive coordinated programmes with disagreements that result in their having to go back to the laboratory, with consequent delay and financial loss. Knowledge of the *mode of action* of a potential new drug obviously greatly enhances prediction from animal studies of what will happen in humans. Whenever practicable, such knowledge should be obtained; sometimes this is quite easy, but sometimes it is impossible. Many drugs have been introduced safely without such knowledge, the later acquisition of which has not always made an important difference to their use (e.g. antimicrobials). Pharmacological studies are integrated with those of the toxicologist to build up a picture of the undesired as well as the desired drug effects.

In *pharmacological testing*, the investigators know what they are looking for and choose the experiments to gain their objectives.

In *toxicological testing*, the investigators have a less clear idea of what they are looking for; they are screening for risk, unexpected as well as predicted, and certain major routines must be done. Toxicity testing is therefore liable to become mindless routine to meet regulatory requirements to a greater extent than the pharmacological studies. The predictive value of special toxicology (above) is particularly controversial. All drugs are poisons if enough is given, and the task of the toxicologist is to find out whether, where and how a compound acts as a poison to animals, and to give an opinion on the significance of the data in relation to risks likely to be run by human beings. This will remain a nearly impossible task until molecular explanations of all effects can be provided.

Toxicologists are in an unenviable position. When a useful drug is safely introduced, they are considered to have done no more than their duty. When an accident occurs, they are invited to explain how this failure of prediction came about. When they predict that a chemical is unsafe in a major way for humans, this prediction is never tested.

ORPHAN DRUGS AND DISEASES

A free-market economy is liable to leave untreated, rare diseases, e.g. some cancers (in all countries), and some common diseases, e.g. parasitic infections (in poor countries).

When a drug is not developed into a usable medicine because the developer will not recover the costs, it is known as an orphan drug, and the disease is an orphan disease; the sufferer is a health orphan.\(^1\) Drugs for rare diseases inevitably must often be licensed on less than ideal amounts of clinical evidence. The remedy for these situations lies in government itself undertaking drug development (which is likely to be inefficient) or in government-offered incentives, such as tax relief, subsidies, exclusive marketing rights, to pharmaceutical companies and, in the case of poor countries, international aid programmes; such programmes are being implemented.\(^1\)

GUIDE TO FURTHER READING


Fears R, Roberts D, Poste G 2000 Rational or rationed medicine? The promise of genetics for improved clinical practice. British Medical Journal 320:933–935


\(^1\)The cost of treating a patient with the rare genetic Gaucher’s liposome storage disease with genetically engineered enzyme is US$145 000–400 000 per annum, according to severity. Who can and will pay? More such situations will occur.

\(^1\)Official recognition of orphan drug status is accorded in the USA (population 240 million) where the relevant disease affects fewer than 200 000 people; in Japan (population 121 million) for fewer than 50 000 people.
Author Query Form

Book: Clinical Pharmacology
Chapter No.: 3

AU1: Cross-references to be added at proof stage
AU2: Cross-references to be added at proof stage
AU3: Cross-references to be added at proof stage
As the number of potential medicines produced increases, the problem of whom to test them on grows. There are two main groups: healthy volunteers and volunteer patients (plus, rarely, non-volunteer patients). Studies in healthy normal volunteers can help to determine the safety, tolerability, pharmacokinetics and, for some drugs (e.g. anticoagulants and anaesthetic agents), their dynamic effect. For most drugs, the dynamic effect and hence therapeutic potential can be investigated only in patients, e.g. drugs for parkinsonism and antimicrobials. These two groups of subjects for drug testing are complementary, not mutually exclusive in drug development. Introduction of novel agents into both groups poses ethical and scientific problems (see below). There are four main reasons why doctors should have grounding in the knowledge and application of the principles of experimental therapeutics:

1. The optimal selection of a specific dose of a drug for a specific patient should be based on good clinical research. To some extent, every new administration to a patient is an exercise in experimental therapeutics.
2. Increasingly, doctors are personally involved.
3. Good therapeutic research alters clinical practice.
4. Such study provides an exercise in ethical and logical thinking.

Plainly, doctors cannot read in detail and evaluate for themselves all the published studies (often hundreds) that might influence their practice. They therefore turn to specialist research articles and abstracts including meta-analyses (see p. 000) for guidance, but readers must approach these critically.

Modern medicine is sometimes accused of callous application of science to human problems and of subordinating the interest of the individual
EVALUATION OF DRUGS IN HUMANS

to those of the group (society). Official regulatory bodies rightly require scientific evaluation of drugs. Drug developers need to satisfy the official regulators and they also seek to persuade an increasingly sophisticated medical profession to prescribe their products. Patients, too, are far more aware of the comparative advantages and limitations of their medicines than they used to be. For these reasons, scientific drug evaluation as described here is likely to increase in volume and the doctors involved will be held responsible for the ethics of what they do, even if they played no personal part in the study design. Therefore, we provide a brief discussion of some relevant ethical aspects (and particularly of the randomised controlled trial).

RESEARCH INVOLVING HUMAN SUBJECTS

The definition of research continues to present difficulties. The distinction between medical research and innovative medical practice derives from the intent. In medical practice the sole intention is to benefit the individual patient consulting the clinician, not to gain knowledge of general benefit, though such knowledge may incidentally emerge from the clinical experience gained. In medical research the primary intention is to advance knowledge so that patients in general may benefit; the individual patient may or may not benefit directly. Consider also the process of audit, which is used extensively to assess performance, e.g. by individual health-care workers, by departments within hospitals or between hospitals. Audit is a systematic examination designed to determine the degree to which an action or set of actions achieves predetermined objectives. It can be used to address, for example, the delivery of service to patients passing through selected areas of a health-care system with the objective of identifying under-performance and improving standards in the future; there is no added intervention in the care that patients receive.

A distinction has been made between research that is therapeutic, i.e. which may actually have a therapeutic effect or provide information that can be used to help the participating subjects, and that which is non-therapeutic, i.e. which provides information that cannot be of direct use to them, e.g. healthy volunteers always and patients sometimes. This is a somewhat artificial separation, because some trials that are ‘therapeutic’, i.e. involve use of new potential medicines, may, by including a placebo in their design, confer no therapeutic benefit for some participants. Research may also be experimental (involving psychologically intrusive or physically invasive intervention) or solely observational (sometimes called non-interventional) (including epidemiology).

Ethics of research in humans

Some dislike the word ‘experiment’ in relation to humans, thinking that its mere use implies a degree of impropriety in what is done. It is better that all should recognise from the true meaning of the word, ‘to ascertain or establish by trial’, that the benefits of modern medicine derive almost wholly from experimentation and that some risk is inseparable from much medical advance.

The issue of (adequately informed) consent is a principal concern for Research Ethics Committees (also called Institutional Review Boards). People have the right to choose for themselves whether or
The ethics of the randomised and placebo controlled trial

History, including recent history, is replete with examples of even the best-intentioned doctors being wrong about the efficacy and safety of (new) treatments. This situation can and should be remedied by the ethical employment of science.

The use of a placebo (or dummy) raises both ethical and scientific issues (see placebo medicines and the placebo effect, Chapter 1). There are clear-cut cases when placebo use would be ethically unacceptable and scientifically unnecessary, e.g. drug trials in epilepsy and tuberculosis, when the control groups comprise patients receiving the best available therapy.

The pharmaceutically inert (placebo) treatment arm of a trial is useful:

- To distinguish the pharmacodynamic effects of a drug from the psychological effects of the act of medication and the circumstances surrounding it, e.g. increased interest by the doctor, more frequent visits, for these latter may have their placebo effect. Placebo responses have been reported in 30–50% of patients with depression and in 30–80% with chronic stable angina pectoris.
- To distinguish drug effects from natural fluctuations in disease that occur with time, e.g. with asthma or hay fever, and other external factors, provided active treatment, if any, can be ethically withheld. This is also called the ‘assay sensitivity’ of the trial.
- To avoid false conclusions. The use of placebos is valuable in Phase I healthy volunteer studies of novel drugs to help determine whether minor but frequently reported adverse events are drug related or not. Although a placebo treatment can pose ethical problems, it is often preferable to the continued use of treatments of unproven efficacy or safety. The ethical dilemma of subjects suffering as a result of receiving a placebo (or ineffective drug) can be overcome by designing clinical trials that provide mechanisms to allow them to be withdrawn (‘escape’) when defined criteria are reached, e.g. blood pressure above levels that represent treatment failure. Similarly, placebo (or new drug) can be added against a background of established therapy; this is called the ‘add on’ design.

---

7 This is the uncertainty principle: the concept that patients entering a randomised therapeutic trial will have equal potential for benefit and risk is referred to as equipoise.
8 The ‘four principles’ approach (above) is widely utilised in biomedical ethics. A full description and an analysis of the contribution of this and other ethical theories to decision-making in clinical, including research, practice can be found in: Beauchamp T L, Childress J F 2001 Principles of biomedical ethics, 5th edn. Oxford University Press, Oxford.
EVALUATION OF DRUGS IN HUMANS

SECTION 1

To provide a result using fewer research subjects. The difference in response when a test drug is compared with a placebo is likely to be greater than that when a test drug is compared with the best current, i.e. active, therapy (see p. 000).

Investigators who propose to use a placebo, or otherwise withhold effective treatment, should specifically justify their intention. The variables to consider are:

- The severity of the disease
- The effectiveness of standard therapy
- Whether the novel drug under test aims to give only symptomatic relief, or has the potential to prevent or slow up an irreversible event, e.g. stroke or myocardial infarction
- The length of treatment

The objective of the trial (equivalence, superiority or non-inferiority; see p. 000). Thus it may be quite ethical to compare a novel analgesic against placebo for 2 weeks in the treatment of osteoarthritis of the hip (with escape analgesics available). It would not be ethical to use a placebo alone as comparator in a 6-month trial of a novel drug in active rheumatoid arthritis, even with escape analgesia.

The precise use of the placebo will depend on the study design, e.g. whether cross-over, when all patients receive placebo at some point in the trial, or parallel group, when only one cohort receives placebo. Generally, patients easily understand the concept of distinguishing between the imagined effects of treatment and those due to a direct action on the body. Provided research subjects are properly informed and give consent freely, they are not the subject of deception in any ethical sense; but a patient given a placebo in the absence of consent is deceived and the right to compensation may not be waived.

Therefore, when giving their informed consent to participate, research subjects should be told whether there is provision for compensation in case of physical injury, and the circumstances in which they or their dependents would receive it.

Payment of subjects in clinical trials

Healthy volunteers are usually paid to take part in a clinical trial. The rationale is that they will not benefit from treatment received and should be compensated for discomfort and inconvenience. There is a fine dividing line between this and a financial inducement, but it is unlikely that more than a small minority of healthy volunteer studies would now take place without a ‘fee for service’ provision, including ‘out of pocket’ expenses. It is all the more important that the sums involved are commensurate with the invasiveness of the investigations and the length of the studies. The monies should be declared and agreed by the ethics committee.

There is an intuitive abreaction by physicians to pay patients (compared with healthy volunteers), because they feel the accusation of inducement testing in rabbits and monkeys at doses up to 500 times those received by the volunteers apparently showed no ill effect. Six of the volunteers quickly became seriously ill and required admission to an intensive care facility with multi-organ failure due to a ‘cytokine release syndrome’, in effect a massive attack on the body’s own tissues. All the volunteers recovered but with some with disability. This toxicity in humans, despite apparent safety in animals, may be due to the specifically humanised nature of the monoclonal antibody. Testing of perceived high-risk new medicines is likely to be subject to particularly stringent regulation in future. See Wood A J J, Darbyshire J 2006 Injury to research volunteers – the clinical research nightmare. New England Journal of Medicine 354:1869–1871.

Injury to research subjects

The question of compensation for accidental (physical) injury due to participation in research is a vexed one. Plainly there are substantial differences between the position of healthy volunteers (whether or not they are paid) and that of patients who may benefit and, in some cases, who may be prepared to accept even serious risk for the chance of gain. There is no simple answer. But the topic must always be addressed in any research carrying risk, including the risk of withholding known effective treatment.

The CIOMS/WHO Guidelines\(^1\) State:

Research subjects who suffer physical injury as a result of their participation are entitled to such financial or other assistance as would compensate them equitably for any temporary or permanent impairment or disability. In the case of death, their dependents are entitled to material compensation. The right to compensation may not be waived.

\(^1\)Injury to participants in clinical trials is uncommon and serious injury is rare. In March 2006, eight healthy young men entered a trial of a humanised monoclonal antibody designed to be an agonist of a particular receptor on T lymphocytes that stimulates their production and activation. This was the first administration to humans; preclinical
or persuasion could be levelled at them, and because they assuage any feeling of taking advantage of the doctor–patient relationship by the hope that the medicines under test may be of benefit to the individual. This is not an entirely comfortable position.  

### RATIONAL INTRODUCTION OF A NEW DRUG TO HUMANS

When studies in animals predict that a new molecule may be a useful medicine, i.e. effective and safe in relation to its benefits, then the time has come to put it to the test in humans. Most doctors will be involved in clinical trials at some stage of their career and need to understand the principles of drug development. When a new chemical entity offers a possibility of doing something that has not been done before or of doing something familiar in a different or better way, it can be seen to be worth testing. But where it is a new member of a familiar class of drug, potential advantage may be harder to detect. Yet these ‘me too’ drugs are often worth testing. Prediction from animal studies of modest but useful clinical advantage is particularly uncertain and, therefore, if the new drug seems reasonably effective and safe in animals it is rational to test it in humans. From the commercial standpoint, the investment in the development of a new drug can be in the order of £500 million, but will be substantially less for a ‘me too’ drug entering an already developed and profitable market.

### PHASES OF CLINICAL DEVELOPMENT

Human experiments progress in a commonsense manner that is conventionally divided into four phases. These phases are divisions of convenience in what is a continuous expanding process. It begins with a small number of subjects (healthy subjects and volunteer patients) closely observed in laboratory settings, and proceeds through hundreds of patients, to thousands before the drug is agreed to be a medicine by a national or international regulatory authority. It is then licensed for general prescribing (though this is by no means the end of the evaluation). The process may be abandoned at any stage for a variety of reasons, including poor tolerability or safety, inadequate efficacy and commercial pressures. The phases are:

- **Phase 1. Human pharmacology** (20 to 50 subjects)
  - healthy volunteers or volunteer patients,
  - pharmacokinetics (absorption, distribution, metabolism, excretion)
  - pharmacodynamics (biological effects) where practicable, tolerability, safety, efficacy.

- **Phase 2. Therapeutic exploration** (50 to 300 subjects)
  - patients
  - pharmacokinetics and pharmacodynamic dose-ranging, in carefully controlled studies for efficacy and safety, which may involve comparison with placebo.

- **Phase 3. Therapeutic confirmation** (randomised controlled trials; 250 to 1000+ subjects)
  - patients
  - efficacy on a substantial scale; safety; comparison with existing drugs.

- **Phase 4. Therapeutic use** (pharmacovigilance, post-licensing studies) (2000 to 10000+ subjects)
  - surveillance for safety and efficacy: further formal therapeutic trials, especially comparisons with other drugs, marketing studies and pharmacoeconomic studies.

### OFFICIAL REGULATORY GUIDELINES AND REQUIREMENTS

For studies in humans (see also Chapter 5) these ordinarily include:

- Studies of pharmacokinetics and (when other manufacturers have similar products) of

---


11Moderate to severe adverse events have occurred in about 0.5% of healthy subjects. See Orme M et al 1989 British Journal of Clinical Pharmacology 27:125; Sibille M et al 1992 European Journal of Clinical Pharmacology 42:393.

12Guidelines for the conduct and analysis of a range of clinical trials in different therapeutic categories are released from time to time by the Committee on Proprietary Medicinal Products (CPMP) of the European Commission. These guidelines apply to drug development in the European Union. Other regulatory authorities issue guidance, e.g. the Food and Drug Administration in the USA, the Ministry of Health, Labour and Welfare in Japan. There has been considerable success in aligning different guidelines across the world through the International Conferences on Harmonisation (ICH). The source for CPMP guidelines is info@mca.gsi.gov.uk or EuroDirect Publications Officer, Medicines Control Agency, Room 10–238, Market Towers, 1 Nine Elms Lane, London SW8 5NQ, UK.
bioequivalence (equal bioavailability) with alternative products.

- **Therapeutic trials** (reported in detail) that substantiate the safety and efficacy of the drug under likely conditions of use, e.g. a drug for long-term use in a common condition will require a total of at least 1000 patients (preferably more), depending on the therapeutic class, of which at least 100 have been treated continuously for about 1 year.

- **Special groups.** If the drug will be used in, for example, the elderly, then elderly people should be studied if there are reasons for thinking they may react to or handle the drug differently. The same applies to children and to pregnant women (who present a special problem), and who, if they are not studied, may be excluded from licensed uses and so become health ‘orphans’. Studies in patients having disease that affects drug metabolism and elimination may be needed, such as patients with impaired liver or kidney function.

- **Fixed-dose combination** products will require explicit justification for each component.

- **Interaction studies** with other drugs likely to be taken simultaneously. Plainly, all possible combinations cannot be evaluated; an intelligent choice, based on knowledge of pharmacodynamics and pharmacokinetics, is made.

- **The application for a licence for general use** (marketing application) should include a draft Summary of Product Characteristics for prescribers. A Patient Information Leaflet must be submitted. These should include information on the form of the product (e.g. tablet, capsule, sustained-release, liquid), its uses, dosage (adults, children, elderly where appropriate), contraindications (strong recommendation), warnings and precautions (less strong), side-effects/adverse reactions, overdose and how to treat it.

The emerging discipline of pharmacogenomics seeks to identify patients who will respond beneficially or adversely to a new drug by defining certain genotypic profiles. Individualised dosing regimens may be evolved as a result. This tailoring of drugs to individuals is consuming huge resources from drug developers but has yet to establish a place in routine drug development.

---

**THERAPEUTIC INVESTIGATIONS**

There are three key questions to be answered during drug development:

- Does it work?
- Is it safe?
- What is the dose?

With few exceptions, none of these is easy to answer definitively within the confines of a pre-registration clinical trials programme. Effectiveness and safety have to be balanced against each other. What may be regarded as ‘safe’ for a new oncology drug in advanced lung cancer would not be so regarded in the treatment of childhood eczema. The use of the term ‘dose’, without explanation, is irrational as it implies a single dose for all patients. Pharmaceutical companies cannot be expected to produce a large array of different doses for each medicine, but the maxim to use the smallest effective dose that results in the desired effect holds true. Some drugs require titration, others have a wide safety margin so that one ‘high’ dose may achieve optimal effectiveness with acceptable safety. There are two classes of endpoint or outcome of a therapeutic investigation:

- **The therapeutic effect itself** (sleep, eradication of infection), i.e. the outcome.

- A **surrogate effect**, a short-term effect that can be reliably correlated with long-term therapeutic benefit, e.g. blood lipids or glucose or blood pressure. A surrogate endpoint might also be a pharmacokinetic parameter, if it is indicative of the therapeutic effect, e.g. plasma concentration of an antiepileptic drug.

Use of surrogate effects presupposes that the disease process is fully understood. They are best justified in diseases for which the true therapeutic effect can be measured only by studying large numbers of patients over many years. Such long-term outcome studies are indeed always preferable but may be impracticable on organisational, financial and sometimes ethical grounds prior to releasing new drugs for general prescription. It is in areas such as these that the techniques of large-scale surveillance for efficacy, as well as for safety, under conditions of ordinary use (below), would be needed to supplement the necessarily smaller and shorter formal therapeutic trials employing surrogate effects. Surrogate endpoints are of particular value in early
drug development to select candidate drugs from a range of agents.

**Therapeutic evaluation**

The aims of therapeutic evaluation are three-fold:

1. To assess the efficacy, safety and quality of new drugs to meet unmet clinical needs
2. To expand the indications for the use of current drugs (or generic drugs\(^{13}\)) in clinical and marketing terms
3. To protect public health over the lifetime of a given drug.

The process of therapeutic evaluation may be divided into pre- and post-registration phases (Table 4.1), the purposes of which are set out below.

When a new drug is being developed, the first therapeutic trials are devised to find out the best that the drug can do under conditions ideal for showing efficacy, e.g. uncomplicated disease of mild to moderate severity in patients taking no other drugs, with carefully supervised administration by specialist doctors. Interest lies particularly in patients who complete a full course of treatment. If the drug is ineffective in these circumstances there is no point in proceeding with an expensive development programme. Such studies are sometimes called *explanatory trials* as they attempt to ‘explain’ why a drug works (or fails to work) in ideal conditions.

If the drug is found useful in these trials, it becomes desirable next to find out how closely the ideal may be approached in the rough and tumble of routine medical practice: in patients of all ages, at all stages of disease, with complications, taking other drugs and relatively unsupervised. Interest continues in all patients from the moment they are entered into the trial and it is maintained if they fail to complete, or even to start, the treatment; the need is to know the outcome in all patients deemed suitable for therapy, not only in those who successfully complete therapy.\(^{14}\)

The reason some drop out may be related to aspects of the treatment and it is usual to analyse these according to the clinicians’ *initial* intention (intention-to-treat analysis), i.e. investigators are not allowed to risk introducing bias by exercising their own judgement as to who should or should not be excluded from the analysis. In these real-life, or ‘naturalistic’, conditions the drug may not perform so well, e.g. minor adverse effects may now cause patient non-compliance, which had been avoided by supervision and enthusiasm in the early trials. These naturalistic studies are sometimes called ‘pragmatic’ trials.

The *methods* used to test the therapeutic value depend on the stage of development, who is conducting the study (a pharmaceutical company, or an academic body or health service at the behest of a regulatory authority), and the *primary endpoint* or *outcome* of the trial. The methods include:

- Formal therapeutic trials
- Equivalence and non-inferiority trials
- Safety surveillance methods

**Formal therapeutic trials** are conducted during Phase 2 and Phase 3 of pre-registration development, and in the post-registration phase to test the drug in new indications. *Equivalence* trials aim to

<table>
<thead>
<tr>
<th>Table 4.1 Process of therapeutic evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-registration</td>
</tr>
<tr>
<td>Purpose of therapeutic evaluation</td>
</tr>
<tr>
<td>Pharmaceutical company</td>
</tr>
<tr>
<td>To select best candidate for development and registration</td>
</tr>
</tbody>
</table>

\(^{13}\)A drug for which the original patent has expired, so that any pharmaceutical company may market it in competition with the inventor. The term ‘generic’ has come to be synonymous with the non-proprietary or approved name (see Chapter 6).

\(^{14}\)Information on both categories (method effectiveness and use effectiveness) is valuable (Sheiner L B, Rubin D B 1995 Intention-to-treat analysis and the goals of clinical trials. Clinical Pharmacology and Therapeutics 57(1)6–15).
show the therapeutic equivalence of two treatments, usually the new drug under development and an existing drug used as a standard active comparator. Equivalence trials may be conducted before or after registration for the first therapeutic indication of the new drug (see p. 000 for further discussion). Safety surveillance methods use the principles of pharmacoepidemiology (see p. 000) and are concerned mainly with evaluating adverse events and especially rare events, which formal therapeutic trials are unlikely to detect.

NEED FOR STATISTICS

In order truly to know whether patients treated in one way are benefited more than those treated in another, it is essential to use numbers. Statistics has been defined as ‘a body of methods for making wise decisions in the face of uncertainty’. Used properly, they are tools of great value for promoting efficient therapy. More than 100 years ago Francis Galton saw this clearly:

The human mind is … a most imperfect apparatus for the elaboration of general ideas … In our general impressions far too great weight is attached to what is marvellous … Experience warns us against it, and the scientific man takes care to base his conclusions upon actual numbers … to devise tests by which the value of beliefs may be ascertained.

CONCEPTS AND TERMS

Hypothesis of no difference

When it is suspected that treatment A may be superior to treatment B and the truth is sought, it is convenient to start with the proposition that the treatments are equally effective – the ‘no difference’ hypothesis (null hypothesis). After two groups of patients have been treated and it has been found that improvement has occurred more often with one treatment than with the other, it is necessary to decide how likely it is that this difference is due to a real superiority of one treatment over the other. To make this decision we need to understand two major concepts, statistical significance and confidence intervals.

A Statistical significance test\(^\text{17}\) such as the Student’s t test or the chi squared (\(^2\)) test will tell how often an observed difference would occur due to chance (random influences) if there is, in reality, no difference between the treatments. Where the statistical significance test shows that an observed difference would occur only five times if the experiment were repeated 100 times, this is often taken as sufficient evidence that the null hypothesis is unlikely to be true. Therefore, the conclusion is that there is (probably) a real difference between the treatments. This level of probability is generally expressed in therapeutic trials as: ‘the difference was statistically significant’, or ‘significant at the 5% level’ or, \(P=0.05\) (\(P\) is the probability based on chance alone). Statistical significance simply means that the result is unlikely to have occurred if there was no genuine treatment difference, i.e. there probably is a difference.

If the analysis reveals that the observed difference, or greater, would occur only once if the experiment were repeated 100 times, the results are generally said to be ‘statistically highly significant’, or ‘significant at the 1% level’ or \(P=0.01\).

Confidence intervals. The problem with the \(P\) value is that it conveys no information on the amount of the differences observed or on the range of possible differences between treatments. A result that a drug produces a uniform 2% reduction in heart rate may well be statistically significant but it is clinically meaningless. What doctors are interested to know is the size of the difference, and what degree of assurance (confidence) they may have in the precision (reproducibility) of this estimate. To obtain this it is necessary to calculate a confidence interval (see Figs 4.1 & 4.2).\(^\text{18}\)

A confidence interval expresses a range of values that contains the true value with 95% (or other chosen percentage) certainty. The range may be broad, indicating uncertainty, or narrow, indicating (relative) certainty. A wide confidence interval occurs


\(^{16}\)Galton F 1879 Generic images. Proceedings of the Royal Institution.


when numbers are small or differences observed are variable and points to a lack of information, whether the difference is statistically significant or not; it is a warning against placing much weight on (or confidence in) the results of small or variable studies. Confidence intervals are extremely helpful in interpretation, particularly of small studies, as they show the degree of uncertainty related to a result. Their use in conjunction with non-significant results may be especially enlightening.  

A finding of 'not statistically significant' can be interpreted as meaning there is no clinically useful difference only if the confidence intervals for the results are also stated in the report and are narrow. If the confidence intervals are wide, a real difference may be missed in a trial with a small number of subjects, i.e. absence of evidence that there is a difference is not the same as showing that there is no difference. Small numbers of patients inevitably give low precision and low power to detect differences.

**Types of error**

The above discussion provides us with information on the likelihood of falling into one of the two principal kinds of error in therapeutic experiments, for the hypothesis that there is no difference between treatments may either be accepted incorrectly or rejected incorrectly.

**Type I error** \((\alpha)\) is the finding of a difference between treatments when in reality they do not differ, i.e. rejecting the null hypothesis incorrectly. Investigators decide the degree of this error which they are pre-

---

**Fig. 4.1** Relationship between significance tests and confidence intervals for the comparisons between a new treatment and control. The treatment differences a, b, c are all in favour of 'New treatment', but superiority is shown only in A and B. In C, superiority has not been shown. This may be because the effect is small and not detected. The result, nevertheless, is compatible with equivalence or non-inferiority. Adequate precision and power are assumed for all the trials.

**Fig. 4.2** Power curves – an illustrative method of defining the number of subjects required in a given study. In practice, the actual number would be calculated from standard equations. In this example the curves are constructed for 16, 40, 100 and 250 subjects per group in a two-limb comparative trial. The graphs can provide three pieces of information: (1) the number of subjects that need to be studied, given the power of the trial and the difference expected between the two treatments; (2) the power of a trial, given the number of subjects included and the difference expected; and (3) the difference that can be detected between two groups of subjects of given number, with varying degrees of power. (With permission from Baber N, Smith R N, Griffin J P, O’Grady J, D’Arcy P F (eds) 1998 Textbook of pharmaceutical medicine, 3rd edn. Queen’s University of Belfast Press, Belfast.)
pared to tolerate on a scale in which 0 indicates complete rejection of the null hypothesis and 1 indicates its complete acceptance; clearly the level for $\alpha$ must be set near to 0. This is the same as the significance level of the statistical test used to detect a difference between treatments. Thus $\alpha$ (or $P = 0.05$) indicates that the investigators will accept a 5% chance that an observed difference is not a real difference.

**Type II error ($\beta$)** is the finding of no difference between treatments when in reality they do differ, i.e. accepting the null hypothesis incorrectly. The probability of detecting this error is often given wider limits, e.g. $\beta = 0.1–0.2$, which indicates that the investigators are willing to accept a 10–20% chance of missing a real effect. Conversely, the power of the study ($1-\beta$) is the probability of avoiding this error and detecting a real difference, in this case 80–90%.

It is up to the investigators to decide the target difference and what probability level (for either type of error) they will accept if they are to use the result as a guide to action.

Plainly, trials should be devised to have adequate precision and power, both of which are consequences of the size of study. It is also necessary to make an estimate of the likely size of the difference between treatments, i.e. the target difference. Adequate power is often defined as giving an 80–90% chance of detecting (at 1–5% statistical significance, $P = 0.01–0.05$) the defined useful target difference (say 15%). It is rarely worth starting a trial that has less than a 50% chance of achieving the set objective, because the power of the trial is too low.

**TYPES OF THERAPEUTIC TRIAL**

A therapeutic trial is:

- a carefully, and ethically, designed experiment with the aim of answering some precisely framed question. In its most rigorous form it demands equivalent groups of patients concurrently treated in different ways or in randomised sequential order in crossover designs. These groups are constructed by the random allocation of patients to one or other treatment ... In principle the method has application with any disease and any treatment. It may also be applied on any scale; it does not necessarily demand large numbers of patients.\(^{21}\)

This is the classical randomised controlled trial (RCT), the most secure method for drawing a causal inference about the effects of treatments. Randomisation attempts to control biases of various kinds when assessing the effects of treatments. RCTs are employed at all phases of drug development and in the various types and designs of trials discussed below. Fundamental to any trial are:

- A hypothesis
- Definition of the primary endpoint
- The method of analysis
- A protocol.

Other factors to consider when designing or critically appraising a trial are the:

- Characteristics of the patients
- General applicability of the results
- Size of the trial
- Method of monitoring
- Use of interim analyses\(^{22}\)
- Interpretation of subgroup comparisons.

The aims of a therapeutic trial, not all of which can be attempted at any one occasion, are to decide:

- Whether a treatment is effective
- The magnitude of that effect (compared with other remedies or placebo)
- The types of patients in whom it is effective
- The best method of applying the treatment (how often, and in what dosage if it is a drug)
- The disadvantages and dangers of the treatment.

**Dose–response Trials.** Response in relation to the dose of a new investigational drug may be explored in all phases of drug development. Dose–response trials serve a number of objectives, of which the following are of particular importance:

- Confirmation of efficacy (hence a therapeutic trial)

\(^{21}\)Bradford Hill A 1977 Principles of medical statistics. Hodder and Stoughton, London. If there is a ‘father’ of the modern scientific therapeutic trial, it is he.

\(^{22}\)Particularly in large-scale outcome trials, an independent data monitoring committee is given access to the results as these are accumulated; the committee is empowered to discontinue a trial if the results show significant advantage or disadvantage to one or other treatment.
Investigation of the shape and location of the dose–response curve
The estimation of an appropriate starting dose
The identification of optimal strategies for individual dose adjustments
The determination of a maximal dose beyond which additional benefit is unlikely to occur.

Superiority, Equivalence And Non-inferiority in Clinical Trials. The therapeutic efficacy of a novel drug is most convincingly established by demonstrating superiority to placebo, or to an active control treatment, or by demonstrating a dose–response relationship (as above).

In some cases, however, the purpose of a comparison is to show not necessarily superiority, but either equivalence or non-inferiority. The objectives of such trials are to avoid the use of a placebo, to explore possible advantages of safety, dosing convenience and cost, and to present an alternative or ‘second-line’ therapy.

Examples of possible outcome in a ‘head to head’ comparison of two active treatments appear in Figure 4.1.

There are in general, two types of equivalence trials in clinical development: bio-equivalence and clinical equivalence. In the former, certain pharmacokinetic variables of a new formulation have to fall within specified (and regulated) margins of the standard formulation of the same active entity. The advantage of this type of trial is that, if bioequivalence is ‘proven’, then proof of clinical equivalence is not required. Proof of clinical equivalence of a generic product to the marketed product can be much more difficult to demonstrate.

DESIGN OF TRIALS

Techniques to avoid bias
The two most important techniques are:

- Randomisation
- Blinding.

Randomisation Introduces a deliberate element of chance into the assignment of treatments to the subjects in a clinical trial. It provides a sound statistical basis for the evaluation of the evidence relating to treatment effects, and tends to produce treatment groups that have a balanced distribution of prognostic factors, both known and unknown. Together with blinding, it helps to avoid possible bias in the selection and allocation of subjects.

Randomisation may be accomplished in simple or more complex ways, such as:

- Sequential assignments of treatments (or sequences in crossover trials)
- Randomising subjects in blocks. This helps to increase comparability of the treatment groups when subject characteristics change over time or there is a change in recruitment policy. It also gives a better guarantee that the treatment groups will be of nearly equal size.
- By dynamic allocation, in which treatment allocation is influenced by the current balance of allocated treatments.

Blinding. The fact that both doctors and patients are subject to bias due to their beliefs and feelings has led to the invention of the double-blind technique, which is a control device to prevent bias from influencing results. On the one hand, it rules out the effects of hopes and anxieties of the patient by giving both the drug under investigation and a placebo (dummy) of identical appearance in such a way that the subject (the first ‘blind’ person) does not know which he or she is receiving. On the other hand, it also rules out the influence of preconceived hopes of, and unconscious communication by, the investigator or observer by keeping him or her (the second ‘blind’ person) ignorant of whether he or she is prescribing a placebo or an active drug. At the

Note also patient preference trials. Conventionally, patients are invited to participate in a clinical trial, give consent and are then randomised to a particular treatment group. In special circumstances, randomisation takes place first, the patients are informed of the treatment to be offered and are allowed to opt for this or another treatment. This is called pre-consent randomisation or ‘pre-randomisation’. In a trial of simple mastectomy versus lumpectomy with or without radiotherapy for early breast cancer, recruitment was slow because of the disfiguring nature of the mastectomy option. A policy of pre-randomisation was then adopted, letting women know the group to which they would be allocated should they consent. Recruitment increased six-fold and the trial was completed, providing sound evidence that survival was as long with the less disfiguring option (Fisher B, Bauer M, Margolese R et al 1985 Five-year results of a randomised clinical trial comparing total mastectomy and segmental mastectomy with and without radiotherapy in the treatment of breast cancer. New England Journal of Medicine 312:665–673). However, the benefit of enhanced recruitment may be limited by potential for introducing bias.
same time, the technique provides another control, a means of comparison with the magnitude of placebo effects. The device is both philosophically and practically sound.24

A non-blind trial is called an open trial.

The double-blind technique should be used wherever possible, and especially for occasions when it might at first sight seem that criteria of clinical improvement are objective when in fact they are not. For example, the range of voluntary joint movement in rheumatoid arthritis has been shown to be influenced greatly by psychological factors, and a moment’s thought shows why, for the amount of pain patients will put up with is influenced by their mental state.

Blinding should go beyond the observer and the observed. None of the investigators should be aware of treatment allocation, including those who evaluate endpoints, assess compliance with the protocol and monitor adverse events. Breaking the blind (for a single subject) should be considered only when the subject’s physician deems knowledge of the treatment assignment essential in the subject’s best interests.

Sometimes the double-blind technique is not possible, because, for example, side-effects of an active drug reveal which patients are taking it or tablets look or taste different; but it never carries a disadvantage (‘only protection against biased data’). It is not, of course, used with new chemical entities fresh from the animal laboratory, whose dose and effects in humans are unknown, although the subject may legitimately be kept in ignorance (single blind) of the time of administration. Single-blind techniques have a place in therapeutics research, but only when the double-blind procedure is impracticable or unethical.

Ophthalmologists are understandably disinclined to refer to the double-blind technique; they call it double-masked.

**SOME COMMON DESIGN CONFIGURATIONS**

**Parallel group design**

This is the most common clinical trial design for confirmatory therapeutic (Phase 3) trials. Subjects are randomised to one of two or more treatment ‘arms’.

These treatments will include the investigational drug at one or more doses, and one or more control treatments such as placebo and/or an active comparator. Parallel group designs are particularly useful in conditions that fluctuate over a short term, e.g. migraine or irritable bowel syndrome, but are also used for chronic stable diseases such as Parkinson’s disease and types of cancer. The particular advantages of the parallel group design are simplicity, the ability to approximate more closely the likely conditions of use, and the avoidance of ‘carry-over effects’ (see below).

**Cross-over design**

In this design, each subject is randomised to a sequence of two or more treatments, and hence acts as his or her own control for treatment comparisons. The advantage of this design is that subject-to-subject variation is eliminated from treatment comparison so that number of subjects is reduced.

In the basic cross-over design each subject receives each of the two treatments in a randomised order. There are variations to this in which each subject receives a subset of treatments or ones in which treatments are repeated within the same subject (to explore the reproducibility of effects).

The main disadvantage of the cross-over design is carry-over, i.e. the residual influence of treatments on subsequent treatment periods. This can be avoided to some extent by separating treatments with a ‘wash-out’ period and, more importantly, by selecting treatment lengths based on a knowledge of the disease and the new medication. The cross-over design is best suited for chronic stable diseases e.g. hypertension, chronic stable angina pectoris, where the baseline conditions are attained at the start of each treatment arm. The pharmacokinetic characteristics of the new medication are also important, the principle being that the plasma concentration at the start of the next dosing period is zero and no dynamic effect can be detected.

**Factorial designs**

In the factorial design, two or more treatments are evaluated simultaneously through the use of varying combinations of the treatments. The simplest example is the $2 \times 2$ factorial design in which subjects are randomly allocated to one of four possible combinations of two treatments A and B. These are: A alone, B alone, A + B, neither A nor

---

B (placebo). The main uses of the factorial design are to:
- make efficient use of clinical trial subjects by evaluating two treatments with the same number of individuals
- examine the interaction of A with B
- establish dose–response characteristics of the combination of A and B when the efficacy of each has been previously established.

**Multicentre trials**
Multicentre trials are carried out for two main reasons. First, they are an efficient way of evaluating a new medication, by accruing sufficient subjects in a reasonable time to satisfy trial objectives. Second, multicentre trials may be designed to provide a better basis for the subsequent generalisation of their findings. Thus they provide the possibility of recruiting subjects from a wide population and of administering the medication in a broad range of clinical settings. Multicentre trials can be used at any phase in clinical development, but are especially valuable when used to confirm therapeutic value in Phase 3.

The main potential problem with a multicentre clinical trial is that heterogeneity of treatment effects between centres may create difficulty in arriving at a single interpretation. This is not as big a problem as it sometimes painted, and large-scale multicentre trials using minimised data collection techniques and simple endpoints have been of immense value in establishing modest but real treatment effects that apply to a large number of patients, e.g. drugs that improve survival after myocardial infarction.

**N-of-1 trials**
Patients give varied treatment responses and the average effect derived from a population sample may not be helpful in expressing the size of benefit or harm for an individual. In the future pharmacogenomics may provide an answer, but in the meantime the best way to settle doubt as to whether a test drug is effective for an individual patient is the n-of-1 trial. This is a cross-over design in which each patient receives two or more administrations of drug or placebo in random manner; the results from individuals can then be displayed. Two conditions apply. First, the disease in which the drug is being tested must be chronic and stable. Second, the treatment effect must wear off rapidly. N-of-1 trials are not used routinely in drug development and, if so, only at the Phase 3 stage.25,26

**Historical controls**
Any temptation simply to give a new treatment to all patients and to compare the results with the past (historical controls) is almost always unacceptable, even with a disease such as leukaemia. The reasons are that standards of diagnosis and treatment change with time, and the severity of some diseases (infections) fluctuates. The general provision stands that controls must be concurrent and concomitant. An exception to this rule is the case–control study (see p. 000).

**SIZE OF TRIALS**
Before the start of any controlled trial it is necessary to decide the number of patients that will be needed to deliver an answer, for ethical as well as practical reasons. This is determined by four factors:

1. The *magnitude* of the difference sought or expected on the primary efficacy endpoint (the target difference). For between-group studies, the focus of interest is the mean difference that constitutes a clinically significant effect.
2. The *variability* of the measurement of the primary endpoint as reflected by the standard deviation of this primary outcome measure. The magnitude of the expected difference (above) divided by the standard deviation of the difference gives the standardised difference (Fig. 4.2).
3. The defined *significance* level, i.e. the level of chance for accepting a Type I ($\alpha$) error. Levels of 0.05 (5%) and 0.01 (1%) are common targets.
4. The *power* or desired probability of detecting the required mean treatment difference, i.e. the level of chance for accepting a Type II ($\beta$) error. For most controlled trials, a power of 80–90% (0.8–0.9) is frequently chosen as adequate, although higher power is chosen for some studies.

It will be intuitively obvious that a small difference in the effect that can be detected between two treatment groups, or a large variability in the

---

measurement of the primary endpoint, or a high significance level (low \( P \) value) or a large power requirement, all act to increase the required sample size. Figure 4.2 gives a graphical representation of how the power of a clinical trial relates to values of clinically relevant standardised difference for varying numbers of trial subjects (shown by the individual curves). It is clear that the larger the number of subjects in a trial, the smaller is the difference that can be detected for any given power value.

The aim of any clinical trial is to have small Type I and II errors, and consequently sufficient power to detect a difference between treatments, if it exists. Of the four factors that determine sample size, the power and significance level are chosen to suit the level of risk felt to be appropriate; the magnitude of the effect can be estimated from previous experience with drugs of the same or similar action; the variability of the measurements is often known from published experiments on the primary endpoint, with or without drug. These data will, however, not be available for novel substances in a new class, and frequently the sample size in the early phase of development is chosen on a more arbitrary basis. As an example, a trial that would detect, at the 5% level of statistical significance, a treatment that raised a cure rate from 75% to 85% would require 500 patients for 80% power.

**Fixed-sample size and sequential designs**

Defining when a clinical trial should end is not as simple as it first appears. In the standard clinical trial the end is defined by the passage of all of the recruited subjects through the complete design. However, it is results and decisions based on the results that matter, not the number of subjects. The result of the trial may be that one treatment is superior to another or that there is no difference. These trials are of fixed sample size. In fact, patients are recruited sequentially, but the results are analysed at a fixed time-point.

The results of this type of trial may be disappointing if they miss the agreed and accepted level of significance.

It is not legitimate, having just failed to reach the agreed level (say, \( P = 0.05 \)), to take in a few more patients in the hope that they will bring \( P \) value down to 0.05 or less, for this is deliberately not allowing chance and the treatment to be the sole factors involved in the outcome, as they should be.

An alternative (or addition) to repeating the fixed-sample size trial is to use a sequential design in which the trial is run until a useful result is reached. These adaptive designs, in which decisions are taken on the basis of results to date, can assess results on a continuous basis as data for each subject become available or, more commonly, on groups of subjects (group sequential design). The essential feature of these designs is that the trial is terminated when a predetermined result is attained and not when the investigator looking at the results thinks it appropriate. Reviewing results in a continuous or interim basis requires formal interim analysis and there are specific statistical methods for handling the data, which need to be agreed in advance. Group sequential designs are especially successful in large long-term trials of mortality or major non-fatal endpoints when safety must be monitored closely.

Interim analyses can reduce the power of statistical significance tests to a serious degree if they are scheduled to occur more than, say, about four times in a trial. Such sequential designs recognise the reality of medical practice and provide a reasonable balance between statistical, medical and ethical needs. It is a necessity to have expert statistical advice when undertaking such trials; poorly designed and executed studies cannot be salvaged after the event.

**SENNITIVITY OF TRIALS**

Definitive therapeutic trials are expensive and tedious, and may be so prolonged that aspects of treatment have been superseded by the time a result is obtained. A single trial, however well designed, executed and analysed, can answer only the question addressed. The regulatory authorities give guidance as to the number and design of trials that, if successful, would lead to a therapeutic claim. But changing clinical practice in the longer term depends on many other factors, of which confirmatory trials in other centres by different investigators under different conditions are an important part.

**META-ANALYSIS**

The two main outcomes for therapeutic trials are to influence clinical practice and, where appropriate, to

---

make a successful claim for a drug with the regulatory authorities. Investigators are eternally optimistic and frequently plan their trials to look for large effects. Reality is different. The results of a planned (or unplanned) series of clinical trials may vary considerably for several reasons, but most significantly because the studies are too small to detect a treatment effect. In common but serious diseases such as cancer or heart disease, however, even small treatment effects can be important in terms of their total impact on public health. It may be unreasonable to expect dramatic advances in these diseases; we should be looking for small effects. Drug developers, too, should be interested not only in whether a treatment works, but also how well and for whom.

The collecting together of a number of trials with the same objective in a systematic review and analysing the accumulated results using appropriate statistical methods is termed meta-analysis. The principles of a meta-analysis are that:

- It should be comprehensive, i.e. include data from all trials, published and unpublished
- Only randomised controlled trials should be analysed, with patients entered on the basis of ‘intention to treat’.
- The results should be determined using clearly defined, disease-specific endpoints (this may involve a re-analysis of original trials).

There are strong advocates and critics of the concept, its execution and interpretation. Arguments that have been advanced against meta-analysis are:

- An effect of reasonable size ought to be demonstrable in a single trial
- Different study designs cannot be pooled
- Lack of accessibility of all relevant studies
- Publication bias (‘positive’ trials are more likely to be published).

In practice, the analysis involves calculating an odds ratio for each trial included in the meta-analysis. This is the ratio of the number of patients experiencing a particular endpoint, e.g. death, and the number who do not, compared with the equivalent figures for the control group. The number of deaths observed in the treatment group is then compared with the number to be expected if it is assumed that the treatment is ineffective, to give the observed minus expected statistic. The treatment effects for all trials in the analysis are then obtained by summing all the ‘observed minus expected’ values of the individual trials to obtain the overall odds ratio. An odds ratio of 1.0 indicates that the treatment has no effect, an odds ratio of 0.5 indicates a halving and an odds ratio of 2.0 indicates a doubling of the risk that patients will experience the chosen endpoint.

From the position of drug development, the general requirement that scientific results have to be repeatable has been interpreted in the past by the Food and Drug Administration (the regulatory agency in the USA) to mean that two well controlled studies are required to support a claim. But this requirement is itself controversial and its relation to a meta-analysis in the context of drug development is unclear.

In clinical practice, and in the era of cost-effectiveness, the use of meta-analysis as a tool to aid medical decision-making and underpinning ‘evidence-based medicine’ is here to stay.

Figure 4.3 shows detailed results from 11 trials in which antiplatelet therapy after myocardial infarction was compared with a control group. The number of vascular events per treatment group is shown in the second and third columns, and the odds ratios with the point estimates (the value most likely to have resulted from the study) are represented by black squares and their 95% confidence intervals (CI) in the fourth column.

The size of the square is proportional to the number of events. The diamond gives the point estimate and CI for overall effect.

### RESULTS: IMPLEMENTATION

The way in which data from therapeutic trials are presented can influence doctors’ perceptions of the advisability of adopting a treatment in their routine practice.
Relative and absolute risk

The results of therapeutic trials are commonly expressed as the percentage reduction of an unfavourable (or percentage increase in a favourable) outcome, i.e. as the relative risk, and this can be very impressive indeed until the figures are presented as the number of individuals actually affected per 100 people treated, i.e. as the absolute risk.

Where a baseline risk is low, a statement of relative risk alone is particularly misleading as it implies large benefit where the actual benefit is small. Thus a reduction of risk from 2% to 1% is a 50% relative risk reduction, but it saves only one patient for every 100 patients treated. But where the baseline is high, say 40%, a 50% reduction in relative risk saves 20 patients for every 100 treated.

Relative risk reductions can remain high (and thus make treatments seem attractive) even when susceptibility to the events being prevented is low (and the corresponding numbers needed to be treated are large). As a result, restricting the reporting of efficacy to just relative risk reductions can lead to great – and

---

Fig. 4.3 A clear demonstration of benefits from meta-analysis of available trial data, when individual trials failed to provide convincing evidence. (Reproduced with permission of Collins R 2001 Lancet 357:373–380.)
at times excessive – zeal in decisions about treatment for patients with low susceptibilities.\(^{31}\)

A real-life example follows:

Antiplatelet drugs reduce the risk of future non-fatal myocardial infarction by 30% [relative risk] in trials of both primary and secondary prevention. But when the results are presented as the number of patients who need to be treated for one nonfatal myocardial infarction to be avoided [absolute risk] they look very different.

In secondary prevention of myocardial infarction, 50 patients need to be treated for 2 years, while in primary prevention 200 patients need to be treated for 5 years, for one nonfatal myocardial infarction to be prevented. In other words, it takes 100 patient-years of treatment in primary prevention to produce the same beneficial outcome of one fewer nonfatal myocardial infarction.\(^{32}\)

Whether a low incidence of adverse drug effects is acceptable becomes a serious issue in the context of absolute risk. Non-specialist doctors, particularly those in primary care, need and deserve clear and informative presentation of therapeutic trial results that measure the overall impact of a treatment on the patient’s life, i.e. on clinically important outcomes such as morbidity, mortality, quality of life, working capacity, fewer days in hospital. Without it, they cannot adequately advise patients, who may themselves be misled by inappropriate use of statistical data in advertisements or on internet sites.

---

### Important aspects of therapeutic trial reports

- Statistical significance and its clinical importance
- Confidence intervals
- Number needed to treat, or absolute risk

---


\(^{32}\)For example, drug therapy for high blood pressure carries risks, but the risks of the disease vary enormously according to severity of disease: ‘Depending on the initial absolute risk, the benefits of lowering blood pressure range from preventing one cardiovascular event a year for about every 20 people treated, to preventing one event for about every 5000–10000 people treated. The level of risk at which treatment should be started is debatable’ (Jackson R, Barham P, Bills I et al 1993 Management of raised blood pressure in New Zealand: a discussion document. British Medical Journal 307:107–110).

\(^{33}\)A systematic error in the selection or randomisation of patients on admission to a trial such that they differ in prognosis, i.e. the outcome is weighted one way or another by the selection, not by the trial.

\(^{34}\)When the interpretation of an observed association between two variables may be affected by a strong influence from a third variable (which may be hidden or unknown). Examples of confounders would be concomitant drug therapy or differences in known risk factors, e.g. smoking, age, sex.

\(^{35}\)Used here for a group of people having a common attribute, e.g. they have all taken the same drug.
Investigation of the question of thromboembolism and the combined oestrogen–progestogen contraceptive pill by means of an observational cohort study required enormous numbers of subjects (the adverse effect is, fortunately, uncommon) followed over years. An investigation into cancer and the contraceptive pill by an observational cohort would require follow-up for 10–15 years. Happily, epidemiologists have devised a partial alternative: the case–control study.

**Case–control studies**

This reverses the direction of scientific logic from a forward-looking, ‘what happens next’ (prospective) to a backward-looking, ‘what has happened in the past’ (retrospective) investigation. The case–control study requires a definite hypothesis or suspicion of causality, such as an adverse reaction to a drug. The investigator assembles a group of patients who have the condition. A control group of people who have not had the reaction is then assembled (matched, e.g. for sex, age, smoking habits) from hospital admissions for other reasons, primary care records or electoral rolls. A complete drug history is taken from each group, i.e. the two groups are ‘followed up’ backwards to determine the proportion in each group that has taken the suspect agent. Case–control studies do not prove causation. They reveal associations and it is up to investigators and critical readers to decide the most plausible explanation.

A case–control study has the advantage that it requires a much smaller number of cases (hundreds) of disease and can thus be done quickly and cheaply. It has the disadvantage that it follows up subjects backwards and there is always suspicion of the intrusion of unknown and so unavoidable biases in the selection of both patients and controls. Here again, independent repetition of the studies, if the results are the same, greatly enhances confidence in the outcome.

**SURVEILLANCE SYSTEMS: PHARMACOVIGILANCE**

When a drug reaches the market, a good deal is known about its therapeutic activity but rather less about its safety when used in large numbers of patients with a variety of diseases, for which they are taking other drugs. The term *pharmacovigilance* refers to the process of identifying and responding to issues of drug safety through the detection in the community of drug effects, usually adverse. Over a number of years increasingly sophisticated systems have been developed to provide surveillance of drugs in the post-marketing phase. For understandable reasons, they are strongly supported by governments. The position has been put thus:

Four kinds of logic can be applied to drug safety monitoring:

- to attempt to follow a complete cohort of (new) drug users for as long as it is deemed necessary to have adequate information.
- to perform special studies in areas which may be predicted to give useful information
- to try to gain experience from regular reporting of suspected adverse drug reactions from health professionals during the regular clinical use of the drug
- to examine disease trends for drug-related causality.

Drug safety surveillance relies heavily on the techniques of pharmacoepidemiology, which include the following.

**Voluntary reporting.** Doctors, nurses and pharmacists are supplied with cards on which to record suspected adverse reaction to drugs. In the UK, this is called the ‘Yellow Card’ system and the Committee on Safety of Medicines collates the results and advises the Medicines and Healthcare products Regulatory Agency of the government. It is recommended that for:

- newer drugs: all suspected reactions should be reported, i.e. any adverse or any unexpected

---

36The Royal College of General Practitioners (UK) recruited 23 000 women takers of the pill and 23 000 controls in 1968 and issued a report in 1973. It found an approximately doubled incidence of venous thrombosis in combined-pill takers (the dose of oestrogen was reduced because of this study).

37For this reason such studies have been named *trohoc* (cohort spelled backwards) studies (Feinstein A 1981 Journal of Chronic Diseases 34:375).

38Experimental cohort studies (i.e. randomised controlled trials) are on firmer ground with regard to causation as there should be only one systematic difference between the groups (i.e. the treatment being studied). In case–control studies the groups may differ systematically in several ways.

event, however minor, that could conceivably be attributed to the drug

established drugs: all serious suspected reactions should be reported, even if the effect is well recognised.

Inevitably the system depends on the intuitions and willingness of those called on to respond. Surveys suggest that no more than 10% of serious reactions are reported. Voluntary reporting is effective for identifying reactions that develop shortly after starting therapy, i.e. at providing early warnings of drug toxicity. Thus, it is the first line in post-marketing surveillance. Reporting is particularly low, however, for reactions with long latency, such as tardive dyskinesia from chronic neuroleptic use. As the system has no limit of quantitative sensitivity, it may detect the rarest events, e.g. those with an incidence of 1:5000–1:10 000. Voluntary systems are, however, unreliable for estimating the incidence of adverse reactions as this requires both a high rate of reporting (the numerator) and a knowledge of the rate of drug usage (the denominator).

Prescription event monitoring. This is a form of observational cohort study. Prescriptions for a drug (say, 20 000) are collected (in the UK this is made practicable by the existence of a National Health Service in which prescriptions are sent to a single central authority for pricing and payment of the pharmacist). The prescriber is sent a questionnaire and asked to report all events that have occurred (not only suspected adverse reactions) with no judgement regarding causality. Thus ‘a broken leg is an event. If more fractures were associated with this drug they could have been due to hypotension, CNS effects or metabolic disease’. By linking general practice and hospital records and death certificates, both prospective and retrospective studies can be done and unsuspected effects detected. Prescription event monitoring can be used routinely on newly licensed drugs, especially those likely to be widely prescribed in general practice, and it can also be implemented quickly in response to a suspicion raised, e.g. by spontaneous reports.

Medical record linkage allows computer correlation in a population of life and health events (birth, marriage, death, hospital admission) with history of drug use. It is being developed as far as resources permit. It includes prescription event monitoring (above). The largest UK medical record linkage is the General Practitioner Research Data Base at the Medicines Control Agency.

Population statistics e.g. birth defect registers and cancer registers. These are insensitive unless a drug-induced event is highly remarkable or very frequent. If suspicions are aroused then case–control and observational cohort studies will be initiated.

STRENGTH OF EVIDENCE

A number of types of clinical investigation are described in this chapter, and elsewhere in the book. When making clinical decisions about a course of therapeutic action, it is obviously relevant to judge the strength of evidence generated by different types of study. This has been summarised as follows, in rank order:

1. Systematic reviews and meta-analysis
2. Randomised controlled trials with definitive results (confidence intervals that do not overlap the threshold of the clinically significant effect)
3. Randomised controlled trials with non-definitive results (a difference that suggests a clinically significant effect but with confidence intervals overlapping the threshold of this effect)
4. Cohort studies
5. Case–control studies
6. Cross-sectional surveys
7. Case reports.

---


42 The reporting of randomised controlled trials has been systemised so that only high-quality studies will be considered. See Moher D, Schulz K F, Altman D G 2001 CONSORT Group. The CONSORT statement: revised recommendations for improving the quality of reports of parallel group randomised trials. Lancet 357:1191–1194.

---

**EVALUATION OF DRUGS IN HUMANS**

**IN CONCLUSION**

Quick, let us prescribe this new drug while it remains effective. Richard Asher.


Greenhalgh T 1997 Papers that report drug trials. British Medical Journal 315:480–483 (see also other articles in the series entitled 'How to read a paper')


Rothwell P M 2005 External validity of randomised controlled trials: ‘to whom do the results of this trial apply?’. Lancet 365:82–93


**GUIDE TO FURTHER READING**


# Author Query Form

**Book:**

**Chapter No.:**

<table>
<thead>
<tr>
<th>Query</th>
<th>Details Required</th>
<th>Author's Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>[AU1]</td>
<td>Cross-reference to be added at proof stage.</td>
<td></td>
</tr>
<tr>
<td>[AU2]</td>
<td>Cross-reference to be added at proof stage.</td>
<td></td>
</tr>
<tr>
<td>[AU3]</td>
<td>Cross-reference to be added at proof stage.</td>
<td></td>
</tr>
<tr>
<td>[AU4]</td>
<td>Cross-reference to be added at proof stage.</td>
<td></td>
</tr>
<tr>
<td>[AU5]</td>
<td>Cross-reference to be added at proof stage.</td>
<td></td>
</tr>
<tr>
<td>[AU6]</td>
<td>Cross-reference to be added at proof stage.</td>
<td></td>
</tr>
<tr>
<td>[AU7]</td>
<td>Cross-reference to be added at proof stage.</td>
<td></td>
</tr>
<tr>
<td>[AU8]</td>
<td>This Figure not cited in the text. Pls. Check.</td>
<td></td>
</tr>
</tbody>
</table>