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Stuart H. Ralston
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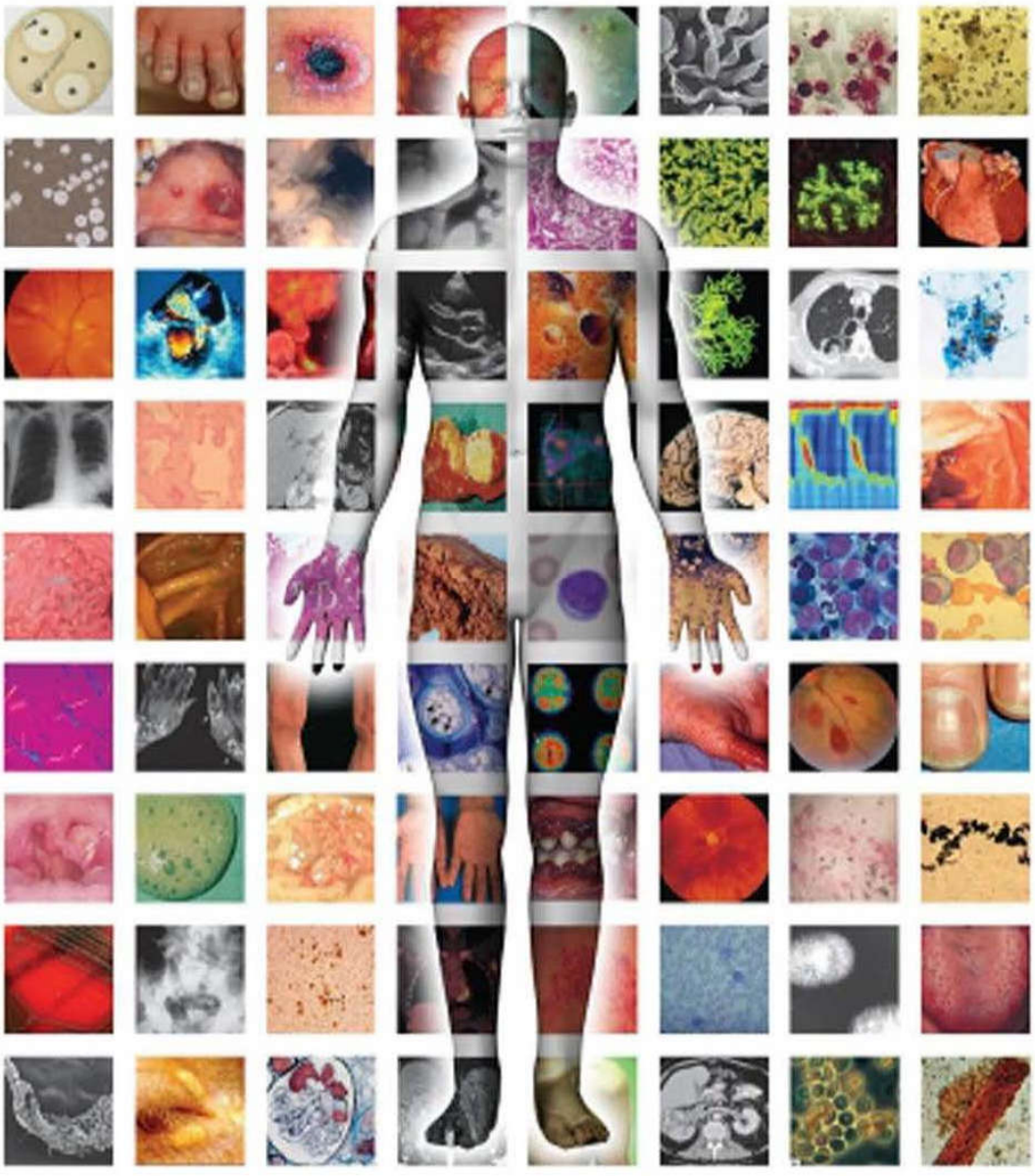
Davidson's Principles and Practice of Medicine

23rd Edition



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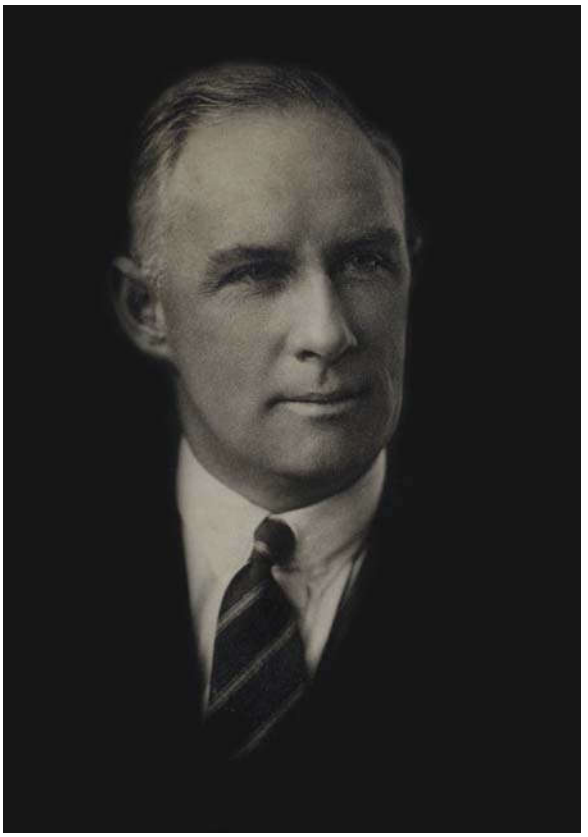

Sir Stanley Davidson (1894–1981)

This famous textbook was the brainchild of one of the great Professors of Medicine of the 20th century. Stanley Davidson was born in Sri Lanka and began his medical undergraduate training at Trinity College, Cambridge; this was interrupted by World War I and later resumed in Edinburgh. He was seriously wounded in battle, and the carnage and shocking waste of young life that he encountered at that time had a profound effect on his subsequent attitudes and values.

In 1930 Stanley Davidson was appointed Professor of Medicine at the University of Aberdeen, one of the first full-time Chairs of Medicine anywhere and the first in Scotland. In 1938 he took up the Chair of Medicine at Edinburgh and was to remain in this post until retirement in 1959. He was a renowned educator and a particularly gifted teacher at the bedside, where he taught that everything had to be questioned and explained. He himself gave most of the systematic lectures in Medicine, which were made available as typewritten notes that emphasised the essentials and far surpassed any textbook available at the time.

Principles and Practice of Medicine was conceived in the late 1940s with its origins in those lecture notes. The first edition, published in 1952, was a masterpiece of clarity and uniformity of style. It was of modest size and price, but sufficiently comprehensive and up to date to provide students with the main elements of sound medical practice. Although the format and presentation have seen many changes in 22 subsequent editions, Sir Stanley's original vision and objectives remain. More than half a century after its first publication, his book continues to inform and educate students, doctors and health professionals all over the world.

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Preface

Well over two million copies of *Davidson's Principles and Practice of Medicine* have been sold since it was first published in 1952. Now in its 23rd Edition, *Davidson's* is regarded as a 'must-have' textbook for thousands of medical students, doctors and health professionals across the world, describing the pathophysiology and clinical features of the most important conditions encountered in the major specialties of adult medicine and explaining how to investigate, diagnose and manage them. The book is the winner of numerous prizes and awards and has been translated into many languages. Taking its origins from Sir Stanley Davidson's much-admired lecture notes, the book has endured because it continues to keep pace with how modern medicine is taught and to provide a wealth of information in an easy-to-read, concise and beautifully illustrated format.

Davidson's strives to ensure that readers can not only recognise the clinical features of a disease but also understand the underlying causes. To achieve this, each chapter begins with a summary of the relevant pre-clinical science, linking pathophysiology with clinical presentation and treatment so that students can use the book from the outset of their medical studies right through to their final examinations and beyond.

The regular introduction of new authors and editors is important for maintaining freshness. On this occasion, Professor Mark Strachan and Dr Richard Hobson have come on board as editors, and 26 new authors have joined our existing contributors to make up an outstanding team of authorities in their respective fields. As well as recruiting authors from around the globe, particularly for topics such as infectious diseases, HIV and envenomation, we welcome members from 17 countries on to our International Advisory Board. These leading experts provide detailed comments that are crucial to our revision of each new edition. A particularly important aspect in planning the revision is for the editors to meet students and faculty in medical schools in those countries where the book is most widely read, so that we can respond to the feedback of our global readership and their tutors. We use this feedback, along with the information we gather via detailed student reviews and surveys, to craft each edition. The authors, editors and publishing team aim to ensure that readers all over the world are best served by a book that integrates medical science with clinical medicine to convey key knowledge and practical advice in an accessible and readable format. The amount of detail is tailored to the needs of medical students working towards their final examinations, as well as candidates preparing for Membership of the Royal Colleges of Physicians (MRCP) or its equivalent.

With this new edition we have introduced several changes in both structure and content. The opening six chapters provide an account of the principles of genetics, immunology, infectious diseases and population health, along with a discussion of the core principles behind clinical decision-making and good prescribing. Subsequent chapters discuss medical emergencies in poisoning, envenomation and environmental medicine, while a new chapter explores common presentations in acute medicine, as well as the recognition and management of the critically ill. The disease-specific chapters that follow cover the major medical specialties, each one thoroughly revised and updated to ensure that readers have access to the 'cutting edge' of medical knowledge and practice. Two new chapters on maternal and adolescent/transition medicine now complement the one on ageing and disease, addressing particular problems encountered at key stages of patients' lives. Medical ophthalmology is also now included as a direct response to readers' requests.

The innovations introduced in recent editions have been maintained and, in many cases, developed. The highly popular 'Clinical Examination' overviews have been extended to the biochemistry, nutrition and dermatology chapters. The 'Presenting Problems' sections continue to provide an invaluable overview of the most common presentations in each disease area. The 'Emergency' and 'Practice Point' boxes have been retained along with the 'In Old Age', 'In Pregnancy' and 'In Adolescence' boxes, which emphasise key practical points in the presentation and management of the elderly, women with medical disorders who are pregnant or planning pregnancy, and teenagers transitioning between paediatric and adult services.

Education is achieved by assimilating information from many sources and readers of this book can enhance their learning experience by using several complementary resources. We are delighted to have a new self-testing companion book entitled *Davidson's Assessment in Medicine*, containing over 1250 multiple choice questions specifically tailored to the contents of *Davidson's*. The long-standing association of *Davidson's* with its sister books, *Macleod's Clinical Examination* (now in its 14th Edition) and *Principles and Practice of Surgery* (7th Edition), still holds good. Our 'family' has also expanded with the publication of *Davidson's Essentials of Medicine*, a long-requested pocket-sized version of the main text; *Davidson's 100 Clinical Cases*, which contains scenarios directly based on our 'Presenting Problems'; and *Macleod's Clinical Diagnosis*, which describes a systematic approach to the differential diagnosis of symptoms and signs. We congratulate the editors and authors of these books for continuing the tradition of easily digested and expertly illustrated texts.

We all take immense pride in continuing the great tradition first established by Sir Stanley Davidson and in producing an outstanding book for the next generation of doctors.

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Edinburgh 2018

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International Advisory Board

Acknowledgements

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Introduction

The opening six chapters of the book, making up Part 1 on 'Fundamentals of Medicine', provide an account of the principles of genetics, immunology, infectious diseases and population health, along with a discussion of the core principles behind clinical decision-making and good prescribing. Subsequent chapters in Part 2, 'Emergency and Critical Care Medicine', discuss medical emergencies in poisoning, envenomation and environmental medicine, while a new chapter explores common presentations in acute medicine, as well as the recognition and management of the critically ill. The third part, 'Clinical Medicine', is devoted to the major medical specialties. Each chapter has been written by experts in the field to provide the level of detail expected of trainees in their discipline. To maintain the book's virtue of being concise, care has been taken to avoid unnecessary duplication between chapters.

The system-based chapters in Part 3 follow a standard format, beginning with an overview of the relevant aspects of clinical examination, followed by an account of functional anatomy, physiology and investigations, then the common presentations of disease, and details of the individual diseases and treatments relevant to that system. In chapters that describe the immunological, cellular and molecular basis of disease, this problem-based approach brings the close links between modern medical science and clinical practice into sharp focus.

The methods used to present information are described below.

Clinical examination overviews

The value of good clinical skills is highlighted by a two-page overview of the important elements of the clinical examination at the beginning of most chapters. The left-hand page includes a mannikin to illustrate key steps in examination of the relevant system, beginning with simple observations and progressing in a logical sequence around the body. The right-hand page expands on selected themes and includes tips on examination technique and interpretation of physical signs. These overviews are intended to act as an aide-mémoire and not as a replacement for a detailed text on clinical examination, as provided in our sister title, *Macleod's Clinical Examination.*

Presenting problems

Medical students and junior doctors must not only assimilate a great many facts about various disorders but also develop an analytical approach to formulating a differential diagnosis and a plan of investigation for patients who present with particular symptoms or signs. In *Davidson*'s this is addressed by incorporating a 'Presenting Problems' section into all relevant chapters. Nearly 250 presentations are included, which represent the most common reasons for referral to each medical specialty.

Boxes

Boxes are a popular way of presenting information and are particularly useful for revision. They are classified by the type of information they contain, using specific symbols.

General Information

These include causes, clinical features, investigations, treatments and other useful information.

Practice Point

There are many practical skills that students and doctors must master. These vary from inserting a nasogastric tube to reading an ECG or X-ray, or interpreting investigations such as arterial blood gases or thyroid function tests. 'Practice Point' boxes provide straightforward guidance on how these and many other skills can be acquired and applied.

Emergency

These boxes describe the management of many of the most common emergencies in medicine.

In Old Age

In many countries, older people comprise 20% of the population and are the chief users of health care. While they contract the same diseases as those who are younger, there are often important differences in the way they present and how they are best managed. Chapter 32, 'Ageing and disease', concentrates on the principles of managing the frailest group who suffer from multiple comorbidity and disability, and who tend to present with non-specific problems such as falls or delirium. Many older people, though, also suffer from specific single-organ pathology. 'In Old Age' boxes are thus included in each chapter and describe common presentations, implications of physiological changes of ageing, effects of age on investigations, problems of

treatment in old age, and the benefits and risks of intervention in older people.

In Pregnancy

Many conditions are different in the context of pregnancy, while some arise only during or shortly after pregnancy. Particular care must be taken with investigations (for example, to avoid radiation exposure to the fetus) and treatment (to avoid the use of drugs that harm the fetus). These issues are highlighted by 'In Pregnancy' boxes distributed throughout the book, which complement the new chapter on maternal medicine.

In Adolescence

Although paediatric medicine is not covered in *Davidson's*, many chronic disorders begin in childhood and adult physicians often contribute to multidisciplinary teams that manage young patients 'in transition' between paediatric and adult health-care services. This group of patients often presents a particular challenge, due to the physiological and psychological changes that occur in adolescence and which can have a major impact on the disease and its management. Adolescents can be encouraged to take over responsibility from their parents/carers in managing their disease, but are naturally rebellious and often struggle to adhere to the impositions of chronic treatment. To highlight these issues, we have introduced a new chapter on adolescent and transition medicine to accompany the 'In Adolescence' boxes that appear in relevant chapters.

Terminology

The recommended International Non-proprietary Names (INNs) are used for all drugs, with the exception of adrenaline and noradrenaline. British spellings have been retained for drug classes and groups (e.g. amphetamines not amfetamines).

Units of measurement

The International System of Units (SI units) is the recommended means of presentation for laboratory data and has been used throughout *Davidson's*. We recognise, though, that many laboratories around the world continue to provide data in non-SI units, so these have been included in the text for the commonly measured analytes. Both SI and non-SI units are also given in Chapter 35, which describes the reference ranges used in Edinburgh's laboratories. It is important to appreciate that these reference ranges may vary from those used in other laboratories.

Finding what you are looking for

A contents list is given on the opening page of each chapter. In addition, the book contains numerous cross-references to help readers find their way around, along with an extensive index. A list of up-to-date reviews and useful websites with links to management guidelines appears at the end of each chapter.

Giving us your feedback

The Editors and Publisher hope that you will find this edition of *Davidson's* informative and easy to use. We would be delighted to hear from you if you have any comments or suggestions to make for future editions of the book. Please contact us by e-mail at: davidson.feedback@elsevier.com. All comments received will be much appreciated and will be considered by the editorial team.

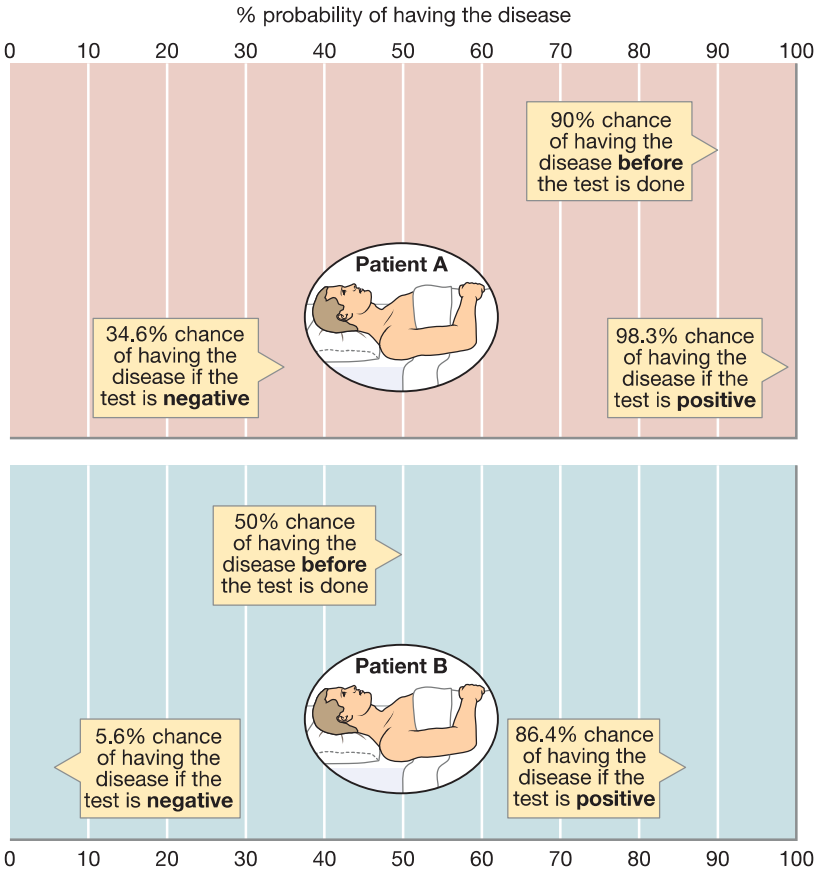

Fig. 1.5 The interpretation of a test result depends on the probability of the disease before the test is carried out. In the example shown, the test being carried out has a sensitivity of 95% and a specificity of 85%. Patient A has very characteristic clinical findings, which make the pre-test probability of the condition for which the test is being used very high – estimated as 90%. Patient B has more equivocal findings, such that the pre-test probability is estimated as only 50%. If the result in Patient A is negative, there is still a significant chance that he has the condition for which he is being tested; in Patient B, however, a negative result makes the diagnosis very unlikely.

Knowing the patient's true state is often unnecessary in clinical decision-making. Sox and colleagues (see 'Further information') argue that there is a difference between knowing that a disease is present and acting as if it were present. The requirement for diagnostic certainty depends on the penalty for being wrong. Different situations require different levels of certainty before starting treatment. How we communicate uncertainty to patients will be discussed later in this chapter (p. 10).

The treatment threshold combines factors such as the risks of the test, and the risks versus benefits of treatment. The point at which the factors are all evenly weighed is the threshold. If a test or treatment for a disease is effective and low-risk (e.g. giving antibiotics for a suspected urinary tract infection), then there is a lower threshold for going ahead. On the other hand, if a test or treatment is less effective or high-risk (e.g. starting chemotherapy for a malignant brain tumour), then greater confidence is required in the clinical diagnosis and potential benefits of treatment first. In principle, if a diagnostic test will not change the management of the patient, then careful consideration should be given to whether it is necessary to do the test at all.

In summary, test results shift our thinking, but rarely give a 'yes' or a 'no' answer in terms of a diagnosis. Sometimes tests shift the probability of disease by less than we realise. Pre-test probability is key, and this is derived from the history and physical examination, combined with a sound knowledge of medicine and an understanding of the prevalence of disease in the particular care setting or the population to which the patient belongs.

Cognitive biases

Advances in cognitive psychology in recent decades have demonstrated that human thinking and decision-making are prone to error. Cognitive biases are subconscious errors that lead to inaccurate judgement and illogical interpretation of information. They are prevalent in everyday life; as the famous saying goes, 'to err is human.'

Take a few moments to look at this simple puzzle. Do not try to solve it mathematically but listen to your intuition:

A bat and ball cost £1.10.
The bat costs £1 more than the ball.
How much does the ball cost?

The answer is at the end of the chapter. Most people get the answer to this puzzle wrong. Two things are going on: one is that humans have two distinct types of processes when it comes to thinking and decision-making – termed 'type 1' and 'type 2' thinking. The other is that the human brain is wired to jump to conclusions sometimes or to miss things that are obvious. British psychologist and patient safety pioneer James

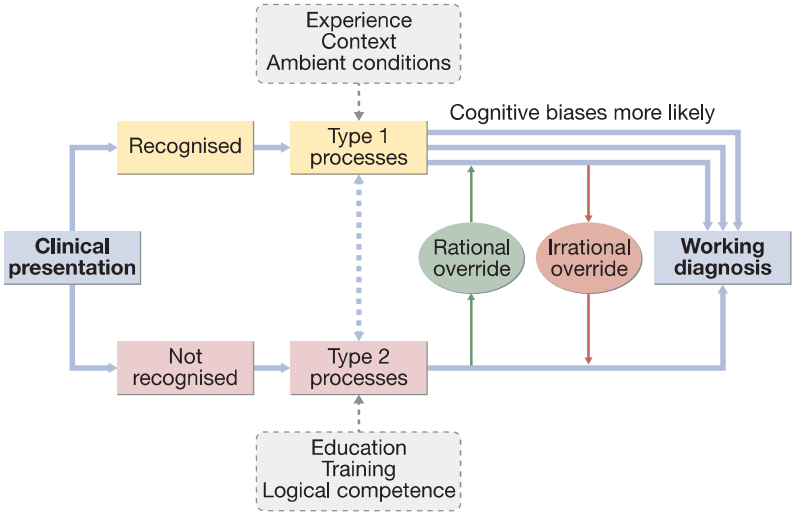

Fig. 1.6 **The interplay between type 1 and type 2 thinking in the diagnostic process.** *Adapted from Croskerry P. A universal model of diagnostic reasoning. Acad Med 2009; 84:1022–1028.*

Reason said that, 'Our propensity for certain types of error is the price we pay for the brain's remarkable ability to think and act intuitively – to sift quickly through the sensory information that constantly bombards us without wasting time trying to work through every situation anew.' This property of human thinking is highly relevant to clinical decision-making.

Type 1 and type 2 thinking

Studies of cognitive psychology and functional magnetic resonance imaging demonstrate two distinct types of processes when it comes to decision-making: intuitive (type 1) and analytical (type 2). This has been termed 'dual process theory'. Box 1.6 explains this in more detail.

Psychologists estimate that we spend 95% of our daily lives engaged in type 1 thinking – the intuitive, fast, subconscious mode of decision-making. Imagine driving a car, for example; it would be impossible to function efficiently if every decision and movement were as deliberate, conscious, slow and effortful as in our first driving lesson. With experience, complex procedures become automatic, fast and effortless. The same applies to medical practice. There is evidence that expert decision-making is well served by intuitive thinking. The problem is that although intuitive processing is highly efficient in many circumstances, in others it is prone to error.

Clinicians use both type 1 and type 2 thinking, and both types are important in clinical decision-making. When encountering a problem that is familiar, clinicians employ pattern recognition and reach a working diagnosis or differential diagnosis quickly (type 1 thinking). When encountering a problem that is more complicated, they use a slower, systematic approach (type 2 thinking). Both types of thinking interplay – they are not mutually exclusive in the diagnostic process. Figure 1.6 illustrates the interplay between type 1 and type 2 thinking in clinical practice.

Errors can occur in both type 1 and type 2 thinking; for example, people can apply the wrong rules or make errors in their application while using type 2 thinking. However, it has been argued that the common cognitive biases encountered in medicine tend to occur when clinicians are engaged in type 1 thinking.

For example, imagine being asked to see a young woman who is drowsy. She is handed over to you as a 'probable overdose' because she has a history of depression and a packet of painkillers was found beside her at home. Her observations show she has a Glasgow Coma Scale score of 10/15, heart rate 100 beats/min, blood pressure 100/60 mmHg, respiratory rate 14 breaths/min, oxygen saturations 98% on air and temperature 37.5°C. Already your mind has reached a working diagnosis. It fits a pattern (type 1 thinking). You think she has taken an overdose. At this point you can stop to think about your thinking (rational override in Fig. 1.6): 'What is the evidence for this diagnosis? What else could it be?'

On the other hand, imagine being asked to assess a patient who has been admitted with syncope. There are several different causes of syncope and a systematic approach is required to reach a diagnosis (type 2 thinking). However, you recently heard about a case of syncope due to a leaking abdominal aortic aneurysm. At the end of your assessment, following evidence-based guidelines, it is clear the patient can be discharged. Despite this, you decide to observe the patient overnight 'just in case' (irrational override in Fig. 1.6). In this example, your intuition is actually availability bias (when things are at the forefront of your mind), which has significantly distorted your estimate of probability.

1.6 Type 1 and type 2 thinking

Type 1	Type 2
Intuitive, heuristic (pattern recognition)	Analytical, systematic
Automatic, subconscious	Deliberate, conscious
Fast, effortless	Slow, effortful
Low/variable reliability	High/consistent reliability
Vulnerable to error	Less prone to error
Highly affected by context	Less affected by context
High emotional involvement	Low emotional involvement
Low scientific rigour	High scientific rigour

Common cognitive biases in medicine

Figure 1.7 illustrates the common cognitive biases prevalent in medical practice. Biases often work together; for example, in

Anchoring The common human tendency to rely too heavily on the first piece of information offered (the 'anchor') when making decisions	**Diagnostic momentum** Once a diagnostic label has been attached to a patient (by the patient or other health-care professionals), it can gather momentum with each review, leading others to exclude other possibilities in their thinking	**Premature closure** The tendency to close the decision-making process prematurely and accept a diagnosis before it, and other possibilities, have been fully explored
Ascertainment bias We sometimes see what we expect to see ('self-fulfilling prophecy'). For example, a frequent self-harmer attends the emergency department with drowsiness; everyone assumes he has taken another overdose and misses a brain injury	**Framing effect** How a case is presented – for example, in handover – can generate bias in the listener. This can be mitigated by always having 'healthy scepticism' about other people's diagnoses	**Psych-out error** Psychiatric patients who present with medical problems are under-assessed, under-examined and under-investigated because problems are presumed to be due to, or exacerbated by, their psychiatric condition
Availability bias Things may be at the forefront of your mind because you have seen several cases recently or have been studying that condition in particular. For example, when one of the authors worked in an epilepsy clinic, all blackouts were possible seizures	**Hindsight bias** Knowing the outcome may profoundly influence the perception of past events and decision-making, preventing a realistic appraisal of what actually occurred – a major problem in learning from diagnostic error	**Search satisficing** We may stop searching because we have found something that fits or is convenient, instead of systematically looking for the best alternative, which involves more effort
Base rate neglect The tendency to ignore the prevalence of a disease, which then distorts Bayesian reasoning. In some cases, clinicians do this deliberately in order to rule out an unlikely but worst-case scenario	**Omission bias** The tendency towards inaction, rooted in the principle of 'first do no harm.' Events that occur through natural progression of disease are more acceptable than those that may be attributed directly to the action of the health-care team	**Triage-cueing** Triage ensures patients are sent to the right department. However, this leads to 'geography is destiny'. For example, a diabetic ketoacidosis patient with abdominal pain and vomiting is sent to surgery. The wrong location (surgical ward) stops people thinking about medical causes of abdominal pain and vomiting
Commission bias The tendency towards action rather than inaction, on the assumption that good can come only from doing something (rather than 'watching and waiting')	**Overconfidence bias** The tendency to believe we know more than we actually do, placing too much faith in opinion instead of gathered evidence	**Unpacking principle** Failure to 'unpack' all the available information may mean things are missed. For example, if a thorough history is not obtained from either the patient or carers (a common problem in geriatric medicine), diagnostic possibilities may be discounted
Confirmation bias The tendency to look for confirming evidence to support a theory rather than looking for disconfirming evidence to refute it, even if the latter is clearly present. Confirmation bias is common when a patient has been seen first by another doctor	**Posterior probability** Our estimate of the likelihood of disease may be unduly influenced by what has gone on before for a particular patient. For example, a patient who has been extensively investigated for headaches presents with a severe headache, and serious causes are discounted	**Visceral bias** The influence of either negative or positive feelings towards patients, which can affect our decision-making

Fig. 1.7 Common cognitive biases in medicine. *Adapted from Croskerry P. Achieving quality in clinical decision-making: cognitive strategies and detection of bias. Acad Emerg Med 2002; 9:1184–1204.*

2.21 Some drugs that require extra caution in patients with renal or hepatic disease

Kidney disease	Liver disease
Pharmacodynamic effects enhanced	
ACE inhibitors and ARBs (renal impairment, hyperkalaemia) Metformin (lactic acidosis) Spironolactone (hyperkalaemia) NSAIDs (impaired renal function) Sulphonylureas (hypoglycaemia) Insulin (hypoglycaemia)	Warfarin (increased anticoagulation because of reduced clotting factor synthesis) Metformin (lactic acidosis) Chloramphenicol (bone marrow suppression) NSAIDs (gastrointestinal bleeding, fluid retention) Sulphonylureas (hypoglycaemia) Benzodiazepines (coma)
Pharmacokinetic handling altered (reduced clearance)	
Aminoglycosides (e.g. gentamicin) Vancomycin Digoxin Lithium Other antibiotics (e.g. ciprofloxacin) Atenolol Allopurinol Cephalosporins Methotrexate Opioids (e.g. morphine)	Phenytoin Rifampicin Propranolol Warfarin Diazepam Lidocaine Opioids (e.g. morphine)

(ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; NSAID = non-steroidal anti-inflammatory drug)

Examples of drugs that require extra caution in patients with renal disease are listed in Box 2.21.

Prescribing for patients with hepatic disease

The liver has a large capacity for drug metabolism and hepatic insufficiency has to be advanced before drug dosages need to be modified. Patients who may have impaired metabolism include those with jaundice, ascites, hypoalbuminaemia, malnutrition or encephalopathy. Hepatic drug clearance may also be reduced in acute hepatitis, in hepatic congestion due to cardiac failure, and in the presence of intrahepatic arteriovenous shunting (e.g. in hepatic cirrhosis). There are no good tests of hepatic drug-metabolising capacity or of biliary excretion, so dosage should be guided by the therapeutic response and careful monitoring for adverse effects. The presence of liver disease also increases the susceptibility to adverse pharmacological effects of drugs. Some drugs that require extra caution in patients with hepatic disease are listed in Box 2.21.

Prescribing for elderly patients

The issues around prescribing in the elderly are discussed in Box 2.22.

Prescribing for women who are pregnant or breastfeeding

Prescribing in pregnancy should be avoided if possible to minimise the risk of adverse effects in the fetus. Drug therapy in pregnancy may, however, be required either for a pre-existing problem (e.g. epilepsy, asthma, hypothyroidism) or for problems that arise during pregnancy (e.g. morning sickness, anaemia, prevention of neural tube defects, gestational diabetes, hypertension). About 35% of women take drug therapy at least once during pregnancy and 6% take drug therapy during the first trimester (excluding iron, folic acid and vitamins). The most commonly used drugs are simple analgesics, antibacterial drugs and antacids. Some considerations when prescribing in pregnancy are listed in Box 2.23.

2.22 Prescribing in old age

- **Reduced drug elimination**: partly due to impaired renal function.
- **Increased sensitivity to drug effects**: notably in the brain (leading to sedation or delirium) and as a result of comorbidities.
- **More drug interactions**: largely as a result of polypharmacy.
- **Lower starting doses and slower dose titration**: often required, with careful monitoring of drug effects.
- **Drug adherence**: may be poor because of cognitive impairment, difficulty swallowing (dry mouth) and complex polypharmacy regimens. Supplying medicines in pill organisers (e.g. dosette boxes or calendar blister packs), providing automatic reminders, and regularly reviewing and simplifying the drug regimen can help.
- **Some drugs that require extra caution, and their mechanisms**:
  - *Digoxin*: increased sensitivity of Na^+/K^+ pump; hypokalaemia due to diuretics; renal impairment favours accumulation → increased risk of toxicity.
  - *Antihypertensive drugs*: reduced baroreceptor function → increased risk of postural hypotension.
  - *Antidepressants, hypnotics, sedatives, tranquillisers*: increased sensitivity of the brain; reduced metabolism → increased risk of toxicity.
  - *Warfarin*: increased tendency to falls and injury and to bleeding from intra- and extracranial sites; increased sensitivity to inhibition of clotting factor synthesis → increased risk of bleeding.
  - *Clomethiazole, lidocaine, nifedipine, phenobarbital, propranolol, theophylline*: metabolism reduced → increased risk of toxicity.
  - *Non-steroidal anti-inflammatory drugs*: poor renal function → increased risk of renal impairment; susceptibility to gastrotoxicity → increased risk of upper gastrointestinal bleeding.

2.23 Prescribing in pregnancy

- **Teratogenesis**: a potential risk, especially when drugs are taken between 2 and 8 weeks of gestation (4–10 weeks from last menstrual period). Common teratogens include retinoids (e.g. isotretinoin), cytotoxic drugs, angiotensin-converting enzyme inhibitors, antiepileptics and warfarin. If there is inadvertent exposure, then the timing of conception should be established, counselling given and investigations undertaken for fetal abnormalities.
- **Adverse fetal effects in late gestation**: e.g. tetracyclines may stain growing teeth and bones; sulphonamides displace fetal bilirubin from plasma proteins, potentially causing kernicterus; opioids given during delivery may be associated with respiratory depression in the neonate.
- **Altered maternal pharmacokinetics**: extracellular fluid volume and V_d increase. Plasma albumin falls but other binding globulins (e.g. for thyroid and steroid hormones) increase. Glomerular filtration increases by approximately 70%, enhancing renal clearance. Placental metabolism contributes to increased clearance, e.g. of levothyroxine and glucocorticoids. The overall effect is a fall in plasma levels of many drugs.
- **In practice**:
  - Avoid any drugs unless the risk:benefit analysis is in favour of treating (usually the mother).
  - Use drugs for which there is some record of safety in humans.
  - Use the lowest dose for the shortest time possible.
  - Choose the least harmful drug if alternatives are available.