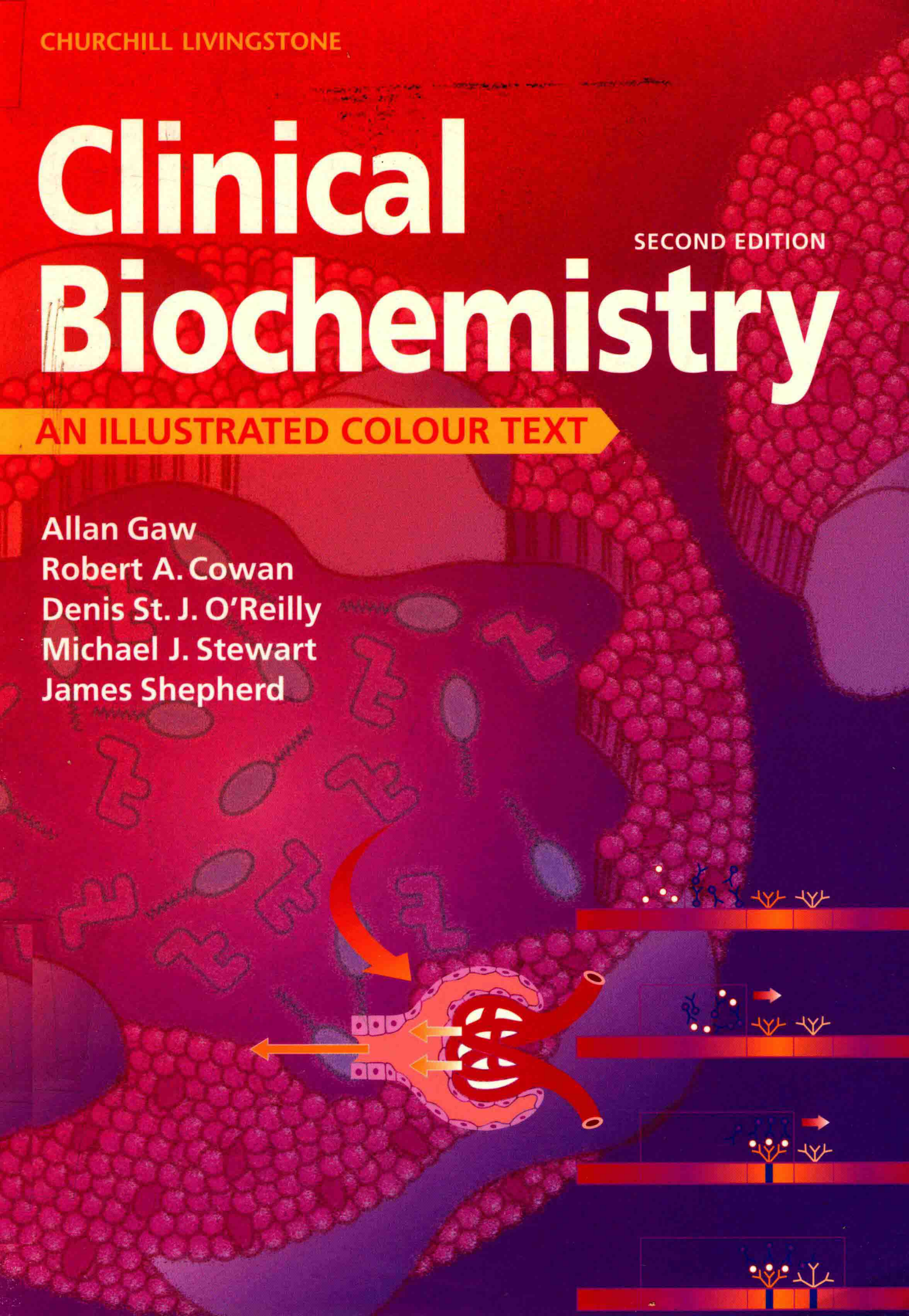
CHURCHILL LIVINGSTONE

Clinical Biochemistry

SECOND EDITION

AN ILLUSTRATED COLOUR TEXT

Allan Gaw
Robert A. Cowan
Denis St. J. O'Reilly
Michael J. Stewart
James Shepherd



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Note to the reader

The reference ranges quoted in this book are for use with the case histories only and should not be used for any other purpose. Each laboratory issues its own reference ranges appropriate to its assay methods and these should always be used in the interpretation of biochemical tests performed in that laboratory.

While every effort has been made to ensure that the drug doses quoted in this book are correct, indications and regimens change with time. Therefore, it remains the responsibility of the reader to check dosage details for each drug on the current data sheet.

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AN ILLUSTRATED COLOUR TEXT

Clinical Biochemistry

PREFACE TO THE FIRST EDITION

Medical education is changing, so the educational tools we use must change too. This book was designed and written for those studying Clinical Biochemistry for the first time. We have placed the greatest emphasis on the foundations of the subject, while covering all those topics found in a medical undergraduate course on Clinical Biochemistry. The format is not that of a traditional textbook. By arranging the subject in double-page learning units we offer the student a practical and efficient way to assimilate the necessary facts, while presenting opportunities for problem solving and self-testing with case histories. Clinical notes present channels for lateral thinking about each learning unit, and boxes summarizing the key points may be used by the student to facilitate rapid revision of the text.

The book is divided into four main sections. *Introducing clinical biochemistry* outlines the background to our subject. In *Core biochemistry* we cover the routine analyses that would form the basic repertoire of most hospital laboratories. The *Endocrinology* section covers thyroid, adrenal, pituitary and gonadal function testing, and in *Specialized investigations* we discuss less commonly requested, but important, analyses.

This book relies on illustrations and diagrams to make many of its points and these should be viewed as integral to the text. The reader is assumed to have a basic knowledge of anatomy, physiology and biochemistry and to be primarily interested in the subject of Clinical Biochemistry from a user's point of view rather than that of a provider. To this end we have not covered analytical aspects except in a few instances where these have direct relevance to the interpretation of biochemical tests. What we have tried to do is present Clinical Biochemistry as a subject intimately connected to Clinical Medicine, placing emphasis on the appropriate use of biochemical tests and their correct interpretation in a clinical setting.

Glasgow
1995

Allan Gaw, Robert A. Cowan,
Denis St. J. O'Reilly,
Michael J. Stewart and James Shepherd

PREFACE TO THE SECOND EDITION

There is a great temptation when writing the second edition of a textbook to start again and write a new first edition. To the authors, perhaps because of their proximity, the original textbook has become a little jaded. However, if we were to believe that we would be ignoring the many letters and communications we have received from teachers and students around the world, all of whom have congratulated us on producing a textbook of Clinical Biochemistry that is interesting, relevant and, above all, easy to access.

In this context the preparation of a new edition takes on a different meaning. To redraft and redesign a successful and useful text book would be nothing short of vandalism. Instead we were charged with updating the outmoded, clarifying the equivocal and correcting the errors which were thankfully very few in the original, but without destroying the spirit of a successful book. If it wasn't broken we didn't fix it. What we have done is make changes to every single double-page spread of the text: some small, some large.

Clinical Biochemistry is a truly international subject, attested to by our global readership and now by the geographical distribution of our authors. Since the first editon was published two of our team have moved away to work in South Africa and Thailand, respectively. Living and working on three different continents has not made the writing of this new edition any easier but it has made it more fun.

In the preface to our first edition we wrote that medical education is changing, so the educational tools we use must change too. Nothing could have been more true. Many medical schools, including our own, have in the last few years switched to a problem based learning approach in the education of their medical students. With this concept comes much that is good. But it also brings a need for a new kind of textbook: one that can integrate the traditional material into a clear clinical context and also place it side by side with information from other specialties. Our first edition of Clinical Biochemistry already had this objective and our new edition continues very much in this vein. We believe this new edition is a significant improvement over the first, but we have not sacrificed what was good about the original for the sake of change.

1998

Allan Gaw, Robert A. Cowan,
Denis St. J. O'Reilly,
Michael J. Stewart and James Shepherd

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INTRODUCING CLINICAL BIOCHEMISTRY

THE CLINICAL BIOCHEMISTRY LABORATORY

Clinical biochemistry, chemical pathology and clinical chemistry are all names for the subject of this book, that branch of laboratory medicine in which chemical and biochemical methods are applied to the study of disease (Fig. 1). While in theory this embraces all non-morphological studies, in practice it is usually, though not exclusively, confined to studies on blood and urine because of the relative ease in obtaining such specimens although analyses are made on other body fluids such as gastric aspirate and cerebrospinal fluid. Clinical biochemical tests comprise over one-third of all hospital laboratory investigations.

THE USE OF BIOCHEMICAL TESTS

Biochemical investigations are involved, to varying degrees, in every branch of clinical medicine. The results of biochemical tests may be of use in diagnosis and in the monitoring of treatment. Biochemical tests may also be of value in screening for disease or in assessing the prognosis once a diagnosis has been made (Fig. 2). The biochemistry laboratory is often involved in research into the biochemical basis of disease and in clinical trials of new drugs.

CORE BIOCHEMISTRY

Biochemical facilities are provided in every hospital, although not necessarily to the same extent. Most biochemistry laboratories provide the 'core analyses', commonly requested tests which are of value in many patients, on a frequent basis (Table 1). The clinician will often request specific groupings of tests, and clinical biochemistry assumes a cryptic language of its own as request forms arrive at laboratory reception for 'U and Es' (urea and electrolytes), 'LFTs' (liver function tests) or 'blood gases'.

SPECIALIZED TESTS

There are a variety of specialties within clinical biochemistry (Table 1). Not every laboratory is equipped to carry out all possible biochemistry requests. Large departments may act as reference centres where less commonly asked for tests are performed. For some tests which are needed in the diagnosis of rare diseases, there may be just one or two laboratories in the country offering the service.

Table 1 **The clinical biochemistry repertoire**

Core biochemical tests	
Sodium, potassium, chloride and bicarbonate	
Urea and creatinine	
Calcium and phosphate	
Total protein and albumin	
Bilirubin and alkaline phosphatase	
Alanine aminotransferase (ALT) and aspartate aminotransferase (AST)	
Thyroxine (T_4) and Thyroid Stimulating Hormone (TSH)	
γ-glutamyl transpeptidase (γGT)	
Creatine kinase (CK)	
H^+, PCO_2 and PO_2 (blood gases)	
Glucose	
Amylase	
Specialized tests	**Emergency tests**
Hormones	Urea and electrolytes
Specific proteins	Blood gases
Trace elements	Amylase
Vitamins	Glucose
Drugs	Salicylate
Lipids and lipoproteins	Paracetamol
DNA analyses	Calcium

THE EMERGENCY LAB

All clinical biochemistry laboratories provide facilities for urgent tests. Only a small number of test types are available from the 'emergency laboratory'. These are processed rapidly and reports phoned

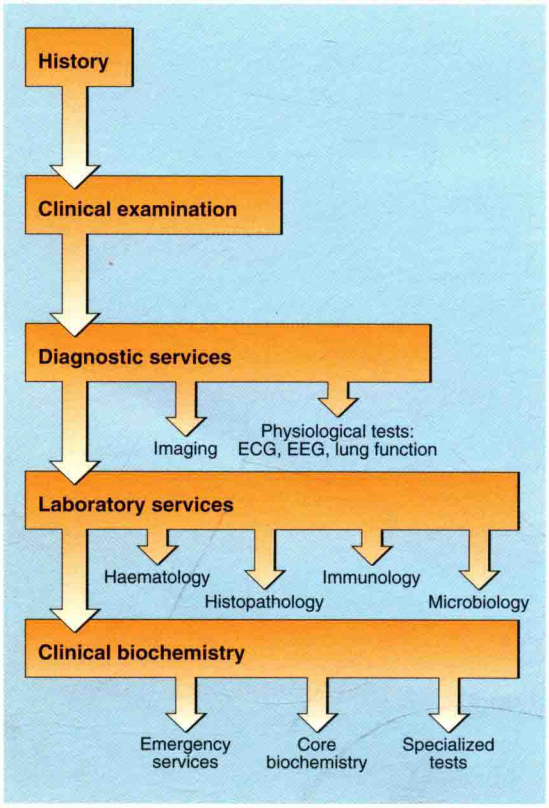


Fig. 1 **The place of clinical biochemistry in medicine.**

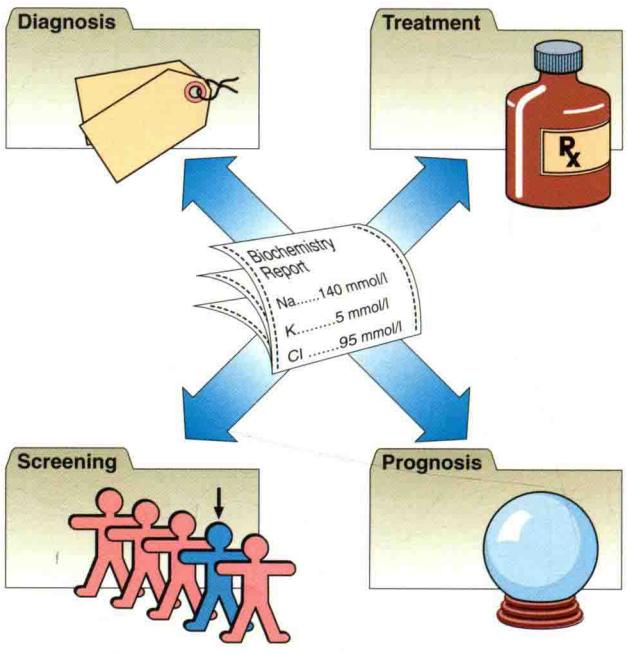
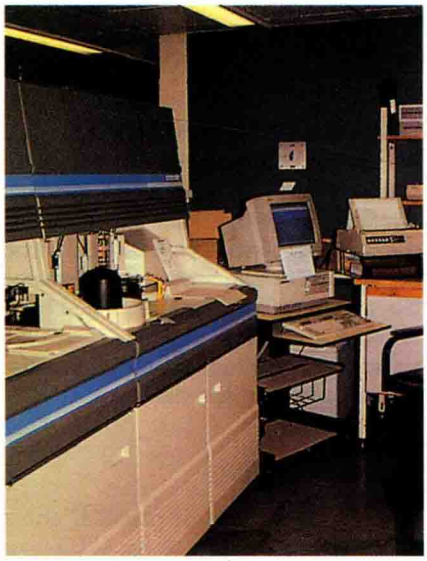
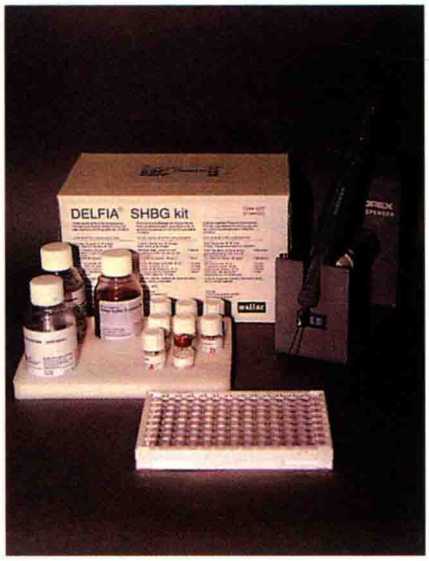


Fig. 2 **How biochemical tests are used.**



(a)



(b)

(c)

Fig. 3 **Analysing the samples: (a)** the automated analyser, **(b)** 'kit' analyses and **(c)** manual methods.

to the requesting clinician or ward. An urgent test is designated as one on which the clinician is likely to take immediate action. An 'on call' service may be provided to ensure that such requests can be done outside the normal working hours of the laboratory. Table 1 shows some of the tests available on an emergency basis.

IN THE OPERATING SUITE OR CLINIC

In some large hospitals, the facilities to perform biochemistry analyses are sited close to where they are needed, for example monitoring of patients undergoing major surgery, such as transplantation, or providing blood glucose results at the diabetic clinic. Many biochemical tests are now being performed away from the laboratory (see pp. 8–9).

AUTOMATION AND COMPUTERIZATION

Most laboratories are now computerized, and the use of bar-coding of specimens and automated methods of analysis allows a high degree of productivity and improves the quality of service. Links to computer terminals on wards and GP surgeries allow direct access to results by the requesting clinician.

TEST REPERTOIRE

There are over 400 different tests which may be carried out in clinical biochemistry laboratories. They vary from the very simple, such as the measurement of sodium, to the highly complex, such as DNA analysis, screening for drugs, or differentiation of lipoprotein variants. Many high volume tests are done on large automated machines. Less frequently performed tests may be conveniently carried out by using commercially prepared reagents packaged in 'kit' form. Some analyses are carried out manually (Fig. 3). Increasing workload, and budgetary constraints, mean that all laboratories continually reassess what is the most cost-effective way of providing the best service.

Dynamic tests require several specimens, timed in relation to a biochemical stimulus, such as a glucose load in the glucose tolerance test for the diagnosis of diabetes mellitus. Some tests provide a clearcut answer to a question; others are only a part of the diagnostic jigsaw.

This book describes how the results of biochemistry analyses are interpreted, rather than how the analyses are performed in the laboratory. An important function of many departments is research and development. Advances in analytical methodology and in our understanding of disease continues to change the test repertoire of the biochemistry department as the value of new tests is appreciated.

LABORATORY PERSONNEL

As well as performing the analyses, the clinical biochemistry laboratory also provides a consultative service. The laboratory has on its staff both medical and scientific personnel who are familiar with the clinical significance and the analytical performance of the test procedures, and they will readily give advice on the interpretation of the results. Do not be hesitant to take advantage of this advice, especially where a case is not straightforward.

Clinical note

The clinical biochemistry laboratory plays only a part in the overall assessment and management of the patient. For some patients, biochemical analyses may have little or no part in their diagnosis or the management of their illness. For others, many tests may be needed before a diagnosis is made, and repeated analyses required to monitor treatment over a long period.

The clinical biochemistry laboratory

- Biochemical tests are used in diagnosis, monitoring treatment, screening and for prognosis.
- Core biochemical tests are carried out in every biochemistry laboratory. Specialized tests may be referred to larger departments. All hospitals provide for urgent tests in the 'emergency laboratory'.
- Laboratory personnel will readily give advice, based on their knowledge and experience, on the use of the biochemistry laboratory, on the appropriate selection of tests, and about the interpretation of results.

THE USE OF THE LABORATORY

Every biochemistry analysis should attempt to answer a question which the clinician has posed about the patient. Obtaining the correct answers can often seem to be fraught with difficulty.

SPECIMEN COLLECTION

In order to carry out biochemical analyses, it is necessary that the laboratory be provided with both the correct specimen for the requested test, and also information which will ensure that the right test is carried out and the result returned to the requesting clinician with the minimum of delay. As much detail as possible should be included on the request form to help both laboratory staff and the clinician in the interpretation of results. This information can be very valuable when assessing a patient's progress over a period, or reassessing a diagnosis. Patient identification must be correct, and the request form should include some indication of the suspected pathology. The requested analyses should be clearly indicated. Request forms differ in design. Clinical biochemistry forms in Europe are conventionally coloured green.

A variety of specimens are used in biochemical analysis and these are shown in Table 1. However, the majority of biochemical tests are performed on serum from venous blood or urine.

Blood specimens

If blood is collected into a plain tube and allowed to clot, after centrifugation a *serum* specimen is obtained (Fig. 1). For many biochemical analyses this will be the specimen recommended. In other cases, especially when the analyte in question is unstable and speed is necessary to obtain a specimen which can be frozen quickly, the blood is collected into a tube containing an anticoagulant such as heparin. When centrifuged, the supernatant is called *plasma* which is almost identical to the cell-free fraction of blood but contains the anticoagulant as well.

Urine specimens

Urine specimen containers may include a preservative to inhibit bacterial growth, or acid to stabilize certain metabolites. They need to be large enough to hold a full 24 h collection. Random urine samples are collected into small 'universal' containers.

Other specimen types

For some tests, specific body fluids or tissue may be required. There will be specific protocols for the handling and transport of these samples to the laboratory. Consult the local lab for advice.

Table 1 **Specimens used for biochemical analyses**

Venous blood, serum or plasma
Arterial blood
Capillary blood
Urine
Faeces
Cerebrospinal fluid (CSF)
Sputum and saliva
Tissue and cells
Aspirates, e.g. pleural fluid ascites joint (synovial) fluid intestinal (duodenal) pancreatic pseudocysts
Calculi (stones)

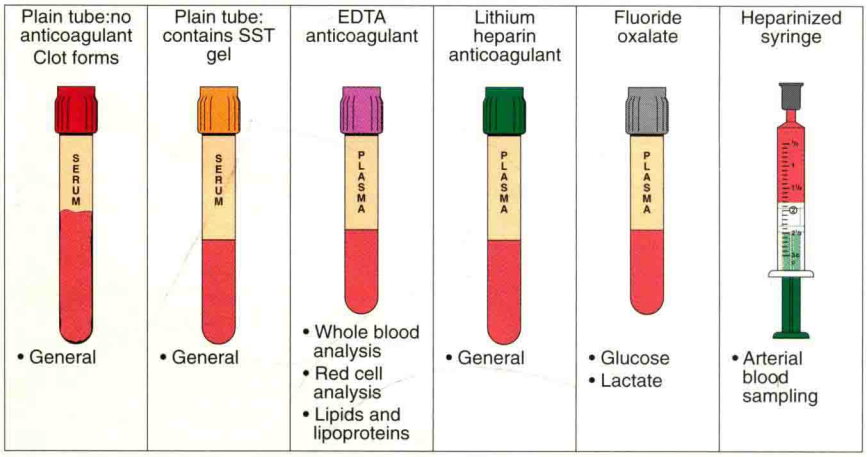


Fig. 1 **Blood specimen tubes for specific biochemical tests.** The colour-coded tubes are the vacutainers in use in the authors' hospital and laboratory.

Dangerous specimens

All specimens from patients with dangerous infections should be labelled with a yellow 'dangerous specimen' sticker. A similar label should be attached to the request form. Of most concern to the laboratory staff are hepatitis B and HIV, but *all* specimens should always be treated both by clinicians and biochemistry staff as potentially hazardous.

SAMPLING ERRORS

There are a number of potential errors which may contribute to the success or failure of the laboratory to provide the correct answers to the clinician's questions. Some of these problems arise when a clinician first obtains specimens from the patient.

- *Blood sampling technique.* Difficulty in obtaining a blood specimen may lead to haemolysis with consequent release of potassium and other red cell constituents. Results for these will be falsely elevated.
- *Prolonged stasis during venepuncture.* Plasma water diffuses into the interstitial space and the serum or plasma sample obtained will be concentrated. Proteins and protein-bound components of plasma such as calcium or thyroxine will be falsely elevated.
- *Insufficient specimen.* Each biochemical analysis requires a certain volume of specimen to enable the test to be carried out. It may prove to be impossible for the laboratory to measure everything requested on a small volume specimen.
- *Errors in timing.* The biggest source of error in the measurement of any analyte in a 24-hour urine specimen is in the collection of an accurately timed volume of urine.
- *Incorrect specimen container.* For many analyses the blood must be collected into a container with anticoagulant and preservative. For example, samples for glucose should be collected into a special container containing fluoride which inhibits glycolysis; otherwise the time taken to deliver the sample to the laboratory can affect the result. If a sample is collected into the wrong container, it should never be decanted into another type of tube. For example, blood which has been exposed even briefly to EDTA (an anticoagulant used in sample containers for lipids) will have a markedly reduced calcium concentration, approaching zero.

- *Inappropriate sampling site.* Blood samples should not be taken 'downstream' from an intravenous drip. It is not unheard of for the laboratory to receive a blood glucose request on a specimen taken from the same arm into which 5% glucose is being infused. Usually the results are biochemically incredible but it is just possible that they may be acted upon, with disastrous consequences for the patient.
- *Incorrect specimen storage.* A blood sample stored overnight before being sent to the laboratory will show falsely high potassium, phosphate and red cell enzymes such as lactate dehydrogenase, because of leakage into the extracellular fluid from the cells.

HOW OFTEN TO INVESTIGATE

Many biochemical tests are repeated at intervals. How often depends on how quickly significant changes are liable to occur, and there is little point in requesting tests if a numerical change will *not* have an influence on treatment.

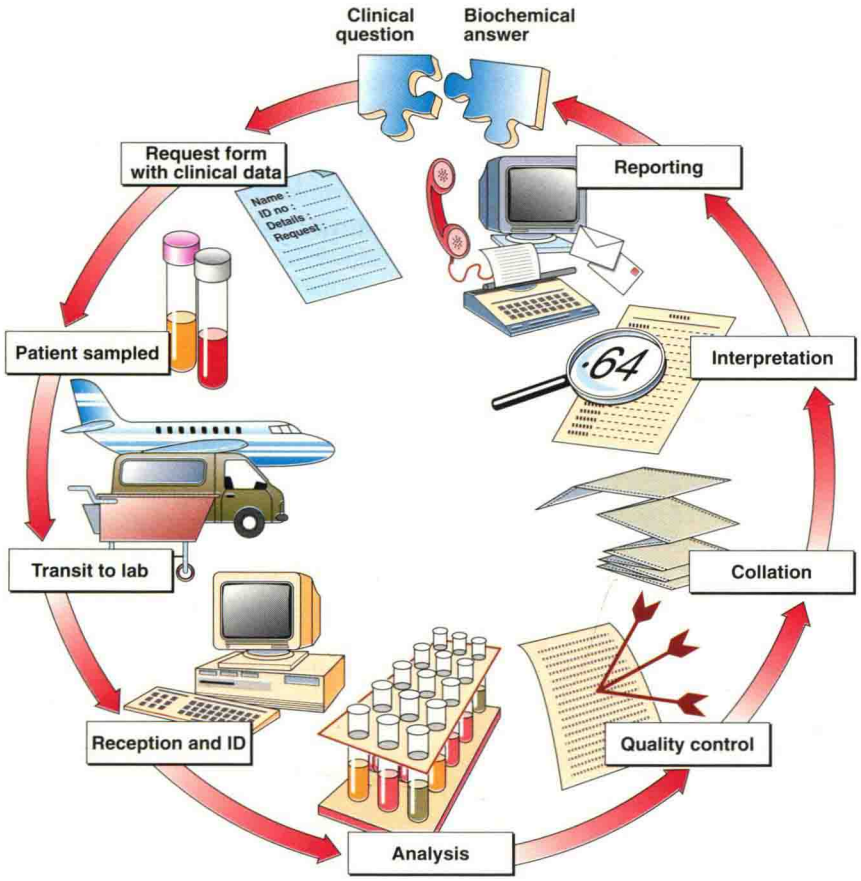


Fig. 2 **Circuit diagram of the clinical biochemistry process.**

URGENT REQUESTS

The main reason for asking for an analysis to be performed on an urgent basis is that immediate treatment depends on the result.

ANALYSING THE SPECIMEN

Once the form and specimen arrive at the laboratory reception, they are matched with a unique identifying number or bar code. The average lab receives many thousands of requests and samples each day and it is important that all are clearly identified and never mixed up. Samples proceed through the laboratory as shown in Figure 2. All analytical procedures are quality controlled and the laboratory strives for reliability.

Once the results are available they are collated and a report is issued. Cumulative reports allow the clinician to see at a glance how the most recent result(s) compare with those tests performed previously, providing an aid to the monitoring of treatment.

UNNECESSARY TESTING

There can be no definite rules about the appropriateness, or otherwise, of laboratory testing because of the huge variety of clinical circumstances which may arise. Clinicians should always bear in mind that in requesting a biochemical test they should be asking a question of the laboratory. If not, both the clinician and the laboratory may be performing unnecessary work, with little benefit to the patient.

Case history 1

A blood specimen was taken from a 65-year-old woman to check her serum potassium concentration as she had been on thiazide diuretics for some time. The GP left the specimen in his car and dropped it off at the laboratory on the way to the surgery the next morning.

Immediately on analysing the sample, the biochemist was on the phone to the GP. Why?

Comment on page 152.

Clinical note

Clinical biochemistry is but one branch of laboratory medicine. Specimens may be required for haematology, microbiology, virology, immunology and histopathology, and all require similar attention to detail in filling out request forms and obtaining the appropriate samples for analysis.

The use of the laboratory

- Each biochemistry test request should be thought of as a question about the patient; each biochemical result as an answer.
- Request forms and specimens must be correctly labelled to ensure that results can be communicated quickly to the clinician.
- Many biochemical tests are performed on serum, the supernatant obtained from centrifugation of clotted blood collected into a plain container. Others require 'plasma', the supernatant obtained when blood is prevented from clotting by an anticoagulant.
- A variety of sampling errors may invalidate results.

THE INTERPRETATION OF RESULTS

THE LABORATORY REPORT

It can take considerable effort, and expense, to produce what may seem to be just numbers on pieces of paper. Understanding what these numbers mean is of crucial importance if the correct diagnosis is to be made, or if the patient's treatment is to be changed.

HOW BIOCHEMICAL RESULTS ARE EXPRESSED

Most biochemical analyses are quantitative, although simple qualitative or semi-quantitative tests such as those for the presence of glucose in urine are commonly encountered in methods used for biochemistry testing away from the laboratory. Many tests measure the amount of the analyte in a small volume of the sample, whether that is blood, plasma, serum, urine or some other fluid or tissue. The test results are commonly expressed in molar units. A mole of any compound always contains 6×10^{23} molecules. Describing how much of an analyte is present in 'moles' indicates how many molecules of the substance are present. Molar units can be converted to mass units; one mole is the molecular weight of the substance in grams.

Results are reported as concentrations, usually in terms of the number of moles in one litre (mol/l) (Table 1).

The concept of concentration is illustrated in Figure 1. The concentration of any analyte in a body compartment is a ratio: the amount of the substance dissolved in a known volume. Changes in concentration can occur for two reasons:

- The amount of the analyte can increase or decrease.
- The volume of fluid in which the analyte is dissolved can similarly change.

Enzymes are not usually expressed in moles but as enzyme activity in 'units'. Enzyme assays are carried out in such a way that the activity measured is directly proportional to the amount of enzyme present. Some hormone measurements are expressed as 'units' by comparison to standard reference preparations of known biological potency. Large molecules such as proteins are reported as grams or milligrams. Blood gas results (PCO_2 or PO_2) are expressed in kilopascals (kPa), the units in which partial pressures are measured.

Table 1 **Molar units**

Mole	Abbreviation	Definition
Millimole	mmol	$x10^{-3}$ of a mole
Micromole	µmol	$x10^{-6}$
Nanomole	nmol	$x10^{-9}$
Picomole	pmol	$x10^{-12}$
Femtomole	fmol	$x10^{-15}$

VARIATION IN RESULTS

Biochemical measurements vary for two reasons. There is analytical variation, and also biological variation.

Laboratory analytical performance

A number of terms describe biochemical results. These include:

- precision and accuracy
- sensitivity and specificity
- quality assurance
- reference ranges.

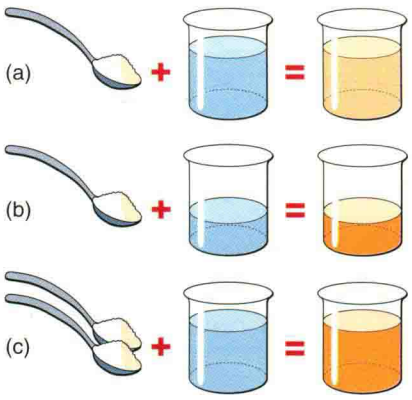


Fig. 1 **Understanding concentrations.** Concentration is always dependent on two factors: the amount of solute and the amount of solvent. The concentration of the sugar solution in the beaker can be increased from 1 spoon/beaker **(a)** to 2 spoons/beaker by either decreasing the volume of solvent **(b)** or increasing the amount of solute **(c)**.

Precision and accuracy

Precision is the reproducibility of an analytical method. Accuracy defines how close the measured value is to the actual value. A good analogy is that of the shooting target. Figure 2 shows the scatter of results which might be obtained by someone with little skill, compared with that of someone with good precision where the results are closely grouped together. Even when the results are all close, they may not hit the centre of the target. Accuracy is therefore poor, as if the 'sights' are off. It is the objective in every biochemical method to have good precision and accuracy.

Sensitivity and specificity

Sensitivity of an assay is a measure of how little of the analyte the method can detect. As new methods are developed they may offer improved detection limits which may help in the discrimination between normal results and those in patients with the suspected disease. Specificity of an assay relates to how good the assay is at discriminating between the requested analyte and potentially interfering substances.

Quality assurance

Every laboratory takes great pains to ensure that the methods in use continue to produce reliable results. Laboratory staff monitor performance of assays using quality control samples to give reassurance that the method is performing satisfactorily with the patients' specimens. These are internal quality controls which are analysed every day or every time an assay is run. The expected values are known and the actual results obtained are compared with previous values to monitor performance. In external quality assurance schemes, identical samples are distributed to laboratories; results are then compared.

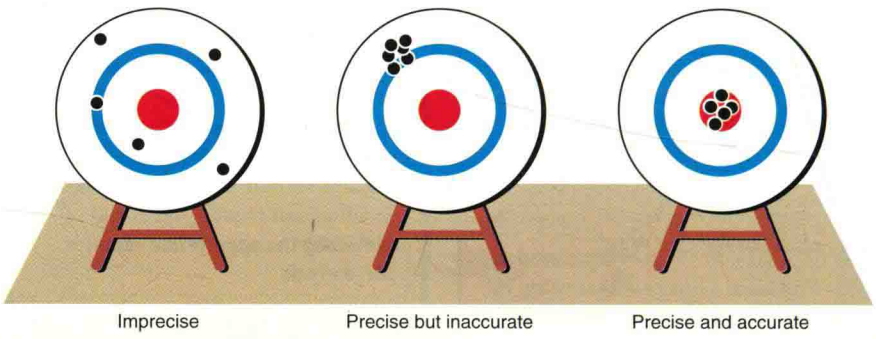


Fig. 2 **Precision and accuracy.**

In this way, the laboratory's own internal standards are themselves assessed.

Reference ranges

Analytical variation is generally less than that from biological variables. Biochemical test results are usually compared to a reference range considered to represent the normal healthy state (Fig. 3). Most reference ranges are chosen arbitrarily to include 95% of the values found in healthy volunteers, and hence, by definition, 5% of the population will have a result outwith the reference range. In practice there are no rigid limits demarcating the diseased population from the healthy; however, the further a result is from the limits of the range, the more likely it is to represent pathology. In some situations it is useful to define 'action limits', where appropriate intervention should be made in response to a biochemical result.

There is often a degree of overlap between the disease state and the 'normal value' (Fig. 4). A patient with an abnormal result who is found not to have the disease is a *false positive*. A patient who has the disease but has a 'normal' result is a *false negative*.

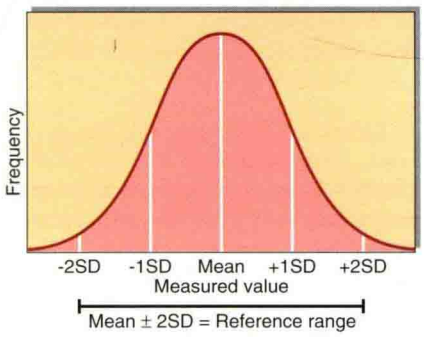


Fig. 3 **Reference range in a normal healthy population.**

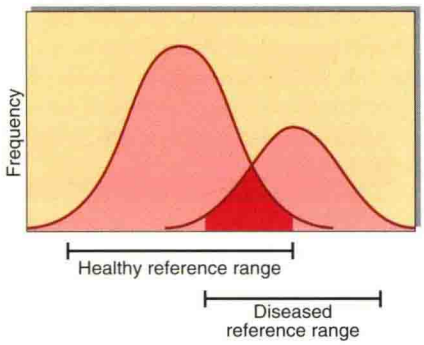


Fig. 4 **Overlap of biochemical results in health and disease.**

Biological factors affecting the interpretation of results

The discrimination between normal and abnormal results is affected by various physiological factors which must be considered when interpreting any given result. These include:

- *Sex of the patient.* Reference ranges for some analytes such as serum creatinine are different for men and women.
- *Age of the patient.* There may be different reference ranges for neonates, children, adults and the elderly.
- *Effect of diet.* The sample may be inappropriate if taken when the patient is fasting or after a meal.
- *Time when sample was taken.* There may be variations during the day and night.
- *Stress and anxiety.* These may affect the analyte of interest.
- *Posture of the patient.* Redistribution of fluid may affect the result.
- *Effects of exercise.* Strenuous exercise can release enzymes from tissues.
- *Medical history.* Infection and/or tissue injury can affect biochemical values independently of the disease process being investigated.
- *Pregnancy.* This alters some reference ranges.
- *Menstrual cycle.* Hormone measurements will vary through the menstrual cycle.
- *Drug history.* Drugs may have specific effects on the plasma concentration of some analytes.

Other factors

When the numbers have been printed on the report form, they still have to be interpreted in the light of a host of variables. Analytical and biological variations have already been considered. Other factors relate to the patient. The clinician can refer to the patient or to the clinical notes, whereas the biochemist has only the information on the request form to consult. The cumulation of biochemistry results is often helpful in patient management.

Case history 2

A serum potassium concentration of 45 mmol/l was recorded in the notes of a 35-year-old man being prepared for appendicectomy. The set of electrolyte results had been phoned from the laboratory. The consultant surgeon was unperturbed, although he did check the results on the ward terminal himself. Why?

Comment on page 152.

The clinician may well ask the following questions on receiving a biochemistry report:

- 'Does the result fit in with what I expected on the basis of the clinical examination and history of the patient?'
- 'If the result is not what I expected, can I explain the discrepancy?'
- 'How can the result change my diagnosis or the way I am managing the patient?'
- 'What should I do next?'

What is done in response to a biochemistry report rests with the clinical judgement of the doctor. There is a maxim that doctors should always 'treat the patient, rather than the laboratory report'. The rest of this book deals with the biochemical investigation of patients and the interpretation of the results obtained.

Clinical note

It is important to realize that an abnormal result does not always indicate that a disease is present, nor a normal result that it is not. Beware of overreacting to the slightly abnormal result in the otherwise healthy individual.

The interpretation of results

- Biochemistry results are often reported as concentrations. Concentrations change if the amount of the analyte changes, or if the volume of solution changes.
- Variability of results is caused by both analytical factors and biological factors.
- The reference range supplied with the test result is only a guide to the probability of the results being statistically 'normal' or 'abnormal'.
- Different reference ranges may apply depending on the age or sex of the patient.
- Sequential changes observed in cumulative reports when placed in clinical context are as important as the absolute value of the result.
- If a result does not accord with that expected for the patient the finding should be discussed with the laboratory reporting office and a repeat test arranged.

BIOCHEMICAL TESTING OUTSIDE THE LABORATORY

INTRODUCTION

The methods for measuring some biological compounds in blood and urine have become so robust and simple to use that measurements can be made away from the laboratory—by the patient's bedside, in the ward sideroom, at the GP's surgery, in the home or even in the shopping centre! Convenience and the desire to know results quickly, as well as expectation of commercial profit by the manufacturers of the tests, have been the major stimuli for these developments. Experience has shown that motivated individuals, e.g. diabetics, frequently perform the tests as well as highly qualified professionals.

The immediate availability of results can enable the appropriate treatment to be instituted quickly. Patients' fears can be allayed. However, it is important to ensure that the limitations of any test and the significance of the results are appreciated by the tester to avoid inappropriate intervention or unnecessary anxiety.

TESTS PERFORMED AWAY FROM THE LABORATORY

Table 1 shows what can be measured in a blood sample outwith the normal laboratory setting. The most common blood test outside the laboratory is the determination of glucose concentration, in a finger stab sample, at home or in the clinic. Diabetic patients who need to monitor their blood glucose on a regular basis can do so at home or at work using one of many commercially available pocket-sized instruments.

Figure 1 shows a portable bench analyser. This instrument may be used to monitor patients' glucose and cholesterol, and is frequently used in many outpatient clinics and in screening centres.

Table 2 lists urine constituents that can be measured away from the laboratory. Many are conveniently measured, semi-quantitatively, using test strips which are dipped briefly into a fresh urine sample. Any excess urine is removed, and the result assessed after a specified time by comparing a colour change with a code on the side of the test strip container. The information obtained from such tests is of variable value to the tester, whether patient or clinician.

The tests commonly performed away from the laboratory can be categorized as follows:

A. *Tests performed in medical or nursing settings.* They clearly give valuable information and allow the practitioner to reassure the patient or family, or initiate further investigations or treatment.
B. *Tests performed in the home, shopping centre or clinical setting.* They can give valuable information when properly and appropriately used.
C. *Alcohol tests.* These are sometimes used to assess fitness to drive. In clinical practice alcohol measurements need to be carefully interpreted. In the Accident and Emergency setting, extreme caution must be taken before one can fully ascribe confusion in a patient with head injury to the effects of alcohol, a common complicating feature in such patients.

Fig. 1 **A portable bench analyser (Courtesy of Boehringer Mannheim GmbH.).**

Table 1 **Common tests on blood performed away from the laboratory**

Analyte	Used when investigating	
Blood gases	Acid–base status	
Glucose	Diabetes mellitus	
Urea	Renal disease	
Creatinine	Renal disease	
Bilirubin	Neonatal jaundice	A*
Therapeutic drugs	Compliance or toxicity	
Salicylate	Detection of poisoning	
Paracetamol	Detection of poisoning	
Glucose	Diabetic monitoring	B*
Cholesterol	Coronary heart disease risk	
Alcohol	Fitness to drive/confusion, coma	C*

Table 2 **Tests on urine performed away from the laboratory**

Analyte	Used when investigating	
Ketones	Diabetic ketoacidosis	
Protein	Renal disease	
Red cells/ haemoglobin	Renal disease	
Bilirubin	Liver disease and jaundice	A*
Urobilinogen	Jaundice/haemolysis	
pH	Renal tubular acidosis	
Glucose	Diabetes mellitus	B*
hCG	Pregnancy test	

**See main text*

METHODOLOGY OF SIDEROOM TESTS

It is a feature of many sideroom tests that their simplicity disguises the use of sophisticated methodology. A home pregnancy test method involves an elegant application of monoclonal antibody technology to detect the human chorionic gonadotrophin (hCG) which is produced by the developing embryo (Fig. 2). The test is simple to carry out; a few drops of urine are placed in the sample window, and the result is shown within five minutes. The addition of the urine solubilizes a mono-clonal antibody for hCG which is covalently bound to tiny blue beads. A second monoclonal, specific for another region of the hCG molecule, is firmly attached in a line at the result window. If hCG is present in the sample it is bound by the first antibody, forming a blue bead–antibody–hCG complex. As the urine diffuses through the strip, any hCG present becomes bound at the second antibody site and this concentrates the

blue bead complex in a line—a positive result. A third antibody recognizes the constant region of the first antibody and binds the excess, thus providing a control to show that sufficient urine had been added to the test strip, the most likely form of error.

GENERAL PROBLEMS

The obvious advantages in terms of time saving and convenience to both patient and clinician must be balanced by a number of possible problems in the use of these tests. They include:

- *Cost.* Many of these tests are expensive alternatives to the traditional methods used in the laboratory. This additional expense must be justified, for example, on the basis of convenience or speed of obtaining the result.
- *Responsibility.* The person performing the assay outwith the laboratory (the operator) must assume a number of responsibilities which would normally be those of the laboratory staff. There is the responsibility to perform the assay appropriately and to provide an answer that is accurate, precise and meaningful. The operator must also record the result, so that others may be able to find it (e.g. in the patient's notes), and interpret the result in its clinical context.

ANALYTICAL PROBLEMS

Many problems under this heading will have little to do with the assay technology but will be due to operator errors. Tests designed for use outwith the laboratory are robust but are by no means foolproof. Most operators will not be trained laboratory technicians but patients, nurses or clinicians. If an assay is to be performed well these individuals must be trained in its use. This may require the reading of a simple set of instructions (e.g. a home pregnancy test) or attending short training sessions (e.g. the ward-based blood gas analyser). The most commonly encountered analytical errors arise because of failure to:

- calibrate an instrument
- clean an instrument
- use quality control materials
- store reagents or strips in appropriate conditions.

All of these problems can be readily overcome by following instructions carefully. Regular maintenance of the equipment may be necessary, and simple quality control checks should be performed. It should always be possible to arrange simple quality control cross checks with the main biochemistry laboratory.

INTERPRETIVE PROBLEMS

Even when analytically correct results are obtained, there are other problems which must be overcome before the exercise can be considered a success. The general appropriateness of the test must be considered. If an assay is performed in an individual of inappropriate age, sex, or at the wrong time of day, or month, then the result may be clinically meaningless.

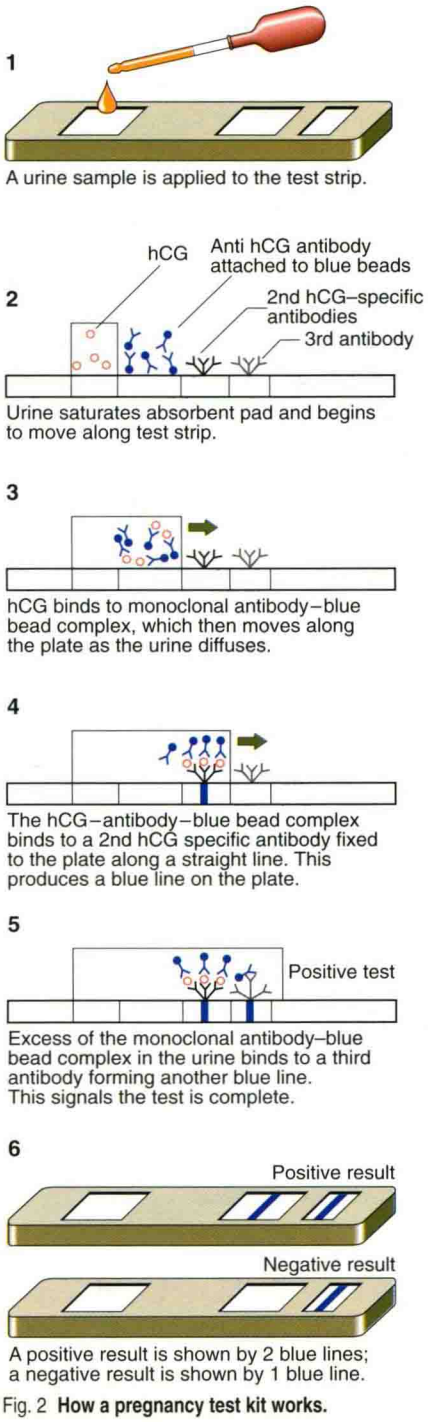


Fig. 2 **How a pregnancy test kit works.**

Similarly, the nature of the sample collected for analysis should be considered when interpreting the result. Where the results seem at odds with the clinical situation, interference from contaminants (e.g. detergents in urine containers) should be considered as should cross reactivity of the assay with more than one analyte (e.g. haemoglobin and myoglobin).

Any biochemical assay takes all these potential problems into account. However, with extra-laboratory testing, correct interpretation of the result is no longer the laboratory's responsibility but that of the operator.

THE FUTURE

There is no doubt that in the future, biochemical testing of patients outside the laboratory will become practical for many of the analytes currently measured in the laboratory. There is, however, likely to be much debate about costs and the clinical usefulness of such non-laboratory based analyses.

Case history 3

At a village fete, a local charity group was fundraising by performing certain side-room tests. An 11-year-old boy was found to have a blood glucose of 14.4 mmol/l. His family was concerned, and an hour later his cousin, a recently diagnosed diabetic, confirmed the hyperglycaemia with his home monitoring equipment, and found glycosuria +++.

- What is the significance of these findings?

Comment on page 152.

Biochemical testing outside the laboratory

- Many biochemical tests are performed outwith the normal laboratory setting, for the convenience of patient and clinician.
- Although apparently simple, such tests may yield erroneous results because of operator errors.
- It is important that advice be readily available to interpret each result in the clinical context.