# A Guide to
# **Diagnostic Clinical Chemistry**

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# Preface

The results of biochemical tests are of little value in the diagnosis and management of disease unless they can be interpreted and understood in terms of the underlying pathophysiology. However, when discussing the interpretative aspects many texts simply provide a list of the causes of abnormal tests, without demonstrating their relationship to the pathophysiology. This book is an attempt to rectify this deficiency, and is based on our experiences in teaching medical students, clinical chemists, technical staff and those who are preparing for professional examinations in medicine, chemical pathology and clinical chemistry.

Each chapter is designed to cover three closely related aspects of its subject. The first part discusses the relevant physiology related to the analyte in question. This section has purposely been kept brief because students using this book will have already acquired the basic knowledge needed, and should therefore need only a reminder of the principles involved. The second section deals with tests and procedures generally available for the investigation and elucidation of specific diagnostic and treatment problems. In this context the relative merits of the tests are critically discussed and reflect our own experiences rather than those found in the literature. The final section of each chapter deals with the pathophysiology of specific disease processes using case material from our own laboratory to illustrate how these processes express themselves in terms of clinical chemistry tests.

We consider that the use of actual patient cases has advantages, in that the quantitative changes in test results caused by disease and its treatment can be experienced at first hand, rather than having to rely on the 'increased, moderately increased' format found in most textbooks. The cases are selected to demonstrate the patterns of results that are most commonly encountered, it not being possible in a short book to illustrate the full range or subtlety of values that may be seen. The variety of cases appearing in individual chapters reflects the availability, and therefore the prevalence, of the particular diseases in our local population. However, we believe that the material covered is broadly representative of that seen by most general hospital laboratories. Obviously some disease processes will not be illustrated because of the scarcity of material. In these instances we have provided a short descriptive summary of

the essential pathophysiology. Certain topics have been excluded, for example vitamins, various paediatric conditions and most inborn errors of metabolism, because they are not normally dealt with in our laboratory.

Each chapter is orientated towards either a single biochemistry test or a group of organ-related tests. We recognize that this approach may elicit criticism on the grounds that many analytes are closely interrelated, and that disturbed homeostasis of one metabolite is invariably associated with abnormalities in others. However, this division was considered appropriate, because in practice the difficult problems in interpretation usually arise when only one of a group of test results is found to be abnormal.

The reference ranges quoted throughout the text are those peculiar to our laboratory and should be used by the reader in this context. For some analytes the reference range quoted with patient cases occasionally changes; this reflects the usual laboratory practice of continually updating the reference values as a consequence of analytical method changes and subtle alterations in the population from which such ranges are derived. For visual clarity in the case examples we have identified tests by a short code (e.g. Amy. for amylase); these codes are used in our laboratory's computerized reporting system and should not be considered as standard abbreviations (see p. ix for full list).

A number of our colleagues have provided us with helpful criticisms and advice during the preparation of the text. For their particular help we wish to thank Drs G. D. Calvert, W. J. Riley, and especially Dr M. D. Guerin and Mrs B. Dilena who read the whole manuscript and provided invaluable comments. Special thanks are due to Mrs Joanna Fenton who typed the drafts and the final manuscript, and to Mr A. Bentley and Mr D. Jones of the Department of Medical Illustration and Media for Figs 9.2, 9.3, and the front cover illustration respectively.

*Adelaide, 1983*

*R. N. Walmsley*
*G. H. White*

# Abbreviations

| | |
|---|---|
| [ ] | Concentration |
| AcAc | Acetoacetic acid |
| ACE | Angiotensin-converting enzyme |
| ACP | Acid phosphatase |
| ACTH | Adrenocorticotropic hormone |
| ADH | Antidiuretic hormone |
| ADP | Adenosine diphosphate |
| αFP | α-Fetoprotein |
| $AHCO_3$ | Actual bicarbonate |
| AIP | Acute intermittent porphyria |
| ALA | Aminolaevulinate |
| Alb. | Albumin |
| Aldo. | Aldosterone |
| ALT | Alanine aminotransferase |
| Amy. | Amylase |
| AP | Alkaline phosphatase |
| AST | Aspartate aminotransferase |
| $\alpha_1$-AT | $\alpha_1$-Antitrypsin |
| ATN | Acute tubular necrosis |
| ATP | Adenosine triphosphate |
| Bili. | Bilirubin |
| BJP | Bence Jones protein |
| BSP | Bromsulpthalein |
| $Ca^{2+}$ | Calcium ion |
| Ca | Total calcium |
| CAH | Chronic active hepatitis |
| CAT | Carnitine acyl transferase |
| CBG | Cortisol-binding globulin (transcortin) |
| CCF | Congestive cardiac failure |
| CEA | Carcinoembryonic antigen |
| CEP | Congenital erythropoietic porphyria |
| Chol. | Cholesterol |
| CK | Creatine kinase |
| Cl | Chloride |
| CNS | Central nervous system |
| COAD | Chronic obstructive airway disease |
| Cort. | Cortisol |

| | |
|---|---|
| CPH | Chronic persistent hepatitis |
| Creat. | Creatinine |
| CRF | Chronic renal failure |
| CSF | Cerebrospinal fluid |
| $1,25\text{-}(OH)_2D_3$ | 1,25-dihydroxycholecalciferol |
| DIT | Diiodotyrosine |
| DOPA | Dihydroxyphenylalanine |
| $E_2$ | Oestradiol |
| EC | Erythropoietic coproporphyria |
| ECF | Extracellular fluid |
| ECV | Extracellular volume |
| EDTA | Ethylenediamine tetra-acetate (sequestrene) |
| EP | Erythropoietic protoporphyria |
| EPP | Electrophoretic pattern |
| EPG | Electrophoretogram |
| ESR | Erythrocyte sedimentation rate |
| Fe | Iron |
| $FE_{Na}$ | Fractional excretion of sodium |
| FFA | Free fatty acid |
| αFP | alpha-fetoprotein |
| FSH | Follicle-stimulating hormone |
| FTI | Free thyroxine index |
| GFR | Glomerular filtration rate |
| GGT | γ-Glutamyltransferase |
| GH | Growth hormone |
| GHRF | Growth hormone releasing factor |
| Glu. | Glucose |
| GnRH | Gonadotropin-releasing hormone |
| GTT | Glucose tolerance test |
| $H^+$ | Hydrogen ion |
| HBD | Hydroxybutyrate dehydrogenase |
| HC | Hereditary coproporphyria |
| $25\text{-}OHD_3$ | 25-Hydroxycholecalciferol |
| HDL | High density lipoprotein |
| HGPRT | Hypoxanthine guanine phosphoribosyl transferase |
| 5 HT | 5-Hydroxytryptamine (serotonin) |
| 5 HIAA | 5-Hydroxyindole acetic acid |
| HMMA | 4-Hydroxy-3-methoxymandelic acid (VMA) |
| HPA | Hypothalamic-pituitary-adrenal axis |
| HPL | Human placental lactogen |
| HVA | Homovanillic acid |

*Abbreviations*

| | |
|---|---|
| ICF | Intracellular fluid |
| IDDM | Insulin-dependent diabetes mellitus |
| IHD | Ischaemic heart disease |
| IM | Intramuscular |
| IV | Intravenous |
| IVV | Intravascular volume |
| K | Potassium |
| 17-KG | 17-Ketogenic steroids |
| LCAT | Lecithin:cholesterol acyl transferase |
| LD | Lactate dehydrogenase |
| LDL | Low density lipoprotein |
| LFT | Liver function tests |
| LH | Luteinizing hormone |
| LHRH | LH-releasing hormone |
| LRH | Low renin hypertension |
| MEN | Multiple endocrine neoplasia |
| Mg | Magnesium |
| MI | Myocardial infarction |
| MIT | Monoiodotyrosine |
| Mol. wt. | Molecular weight |
| Na | Sodium |
| NIDDM | Non insulin-dependent diabetes mellitus |
| 5'NT | 5'-Nucleotidase |
| $NAD^+$ | Nicotinamide-adenine dinucleotide |
| NADH | Nicotinamide-adenine dinucleotide (reduced) |
| OAF | Osteoclast activating factor |
| OGTT | Oral glucose tolerance test |
| 17-OHCS | 17-Hydroxycorticosteroids |
| β-OHB | β-Hydroxybutyric acid |
| OP | Osmotic pressure |
| Osmo. | Osmolality |
| 17-Oxo. | 17-Oxosteroids |
| PBG | Porphobilinogen |
| PCT | Porphyria cutanea tarda |
| $Pco_2$ | Partial pressure of carbon dioxide |
| PG | Prostaglandin |
| PIF | Prolactin inhibitory factor |
| $Po_2$ | Partial pressure of oxygen |
| $PO_4$ | Inorganic phosphate |
| PRA | Plasma renin activity |
| PRF | Prolactin releasing factor |
| PRL | Prolactin |

| | |
|---|---|
| PRPP | Phosphoribosyl pyrophosphate |
| PRU | Prerenal uraemia |
| PTH | Parathyroid hormone |
| RBF | Renal blood flow |
| SI | Système International |
| SIAD | Syndrome of inappropriate antidiuresis |
| SIADH | Syndrome of inappropriate secretion of ADH |
| SD | Standard deviation |
| $T_3$ | Triiodothyronine |
| $T_4$ | Thyroxine |
| TBG | Thyroxine-binding globulin |
| TBP | Thyroxine-binding protein |
| TBPA | Thyroxine-binding prealbumin |
| TCA | Tricarboxylic acid cycle |
| Te | Testosterone |
| TIBC | Total iron binding capacity |
| TP | Total protein |
| TRH | Thyrotropin-releasing hormone |
| Trig. | Triglyceride |
| TSH | Thyroid-stimulating hormone |
| UDP | Uridine diphosphate |
| UV | Ultraviolet light |
| VIP | Vasoactive intestinal peptide |
| VLDL | Very low density lipoprotein |
| VMA | Vanillyl mandelic acid (HMMA) |
| VP | Variegate porphyria |
| ↑ | Increase |
| ↑↑ | Large increase |
| ↓ | Decrease |
| ↓↓ | Large decrease |

# Contents

# 1 Introduction to the interpretation of tests

Diagnostic clinical chemistry uses biochemical knowledge and techniques to assist in the diagnosis of human disease, to follow its progress and to monitor the effect of treatment. The practice of this discipline involves the equal participation of the medical practitioner and the clinical chemist. Until perhaps 20 years ago the limited biochemical knowledge and the small range of available tests usually kept the working relationship between the doctor and the clinical chemist a simple one; the doctor ordered the test and took the patient sample, the biochemist did the test and reported the result (Fig. 1.1).

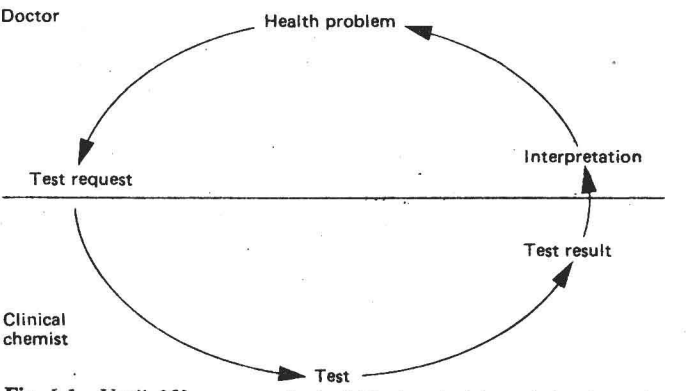


**Fig. 1.1** Until 20 years ago limited biochemical knowledge kept the working relationship between doctor and clinical chemist a simple one.

However, the explosion of new biochemical knowledge, techniques and instrumentation capabilities over the last two decades has brought a matching degree of complication to the early professional relationship. At the practical level it is now often the case that 10 or 15 different nursing, technical and other staff have interposed themselves into the once simple request–test–result chain of events. A typical organization for an average size clinical chemistry laboratory might be as shown in Fig. 1.2.

Before a result is interpreted for clinical purposes the doctor must be confident that the requested test has been performed on the correct patient, and that the result is unaffected by extraneous factors. The clinical chemist also wishes to be similarly confident.

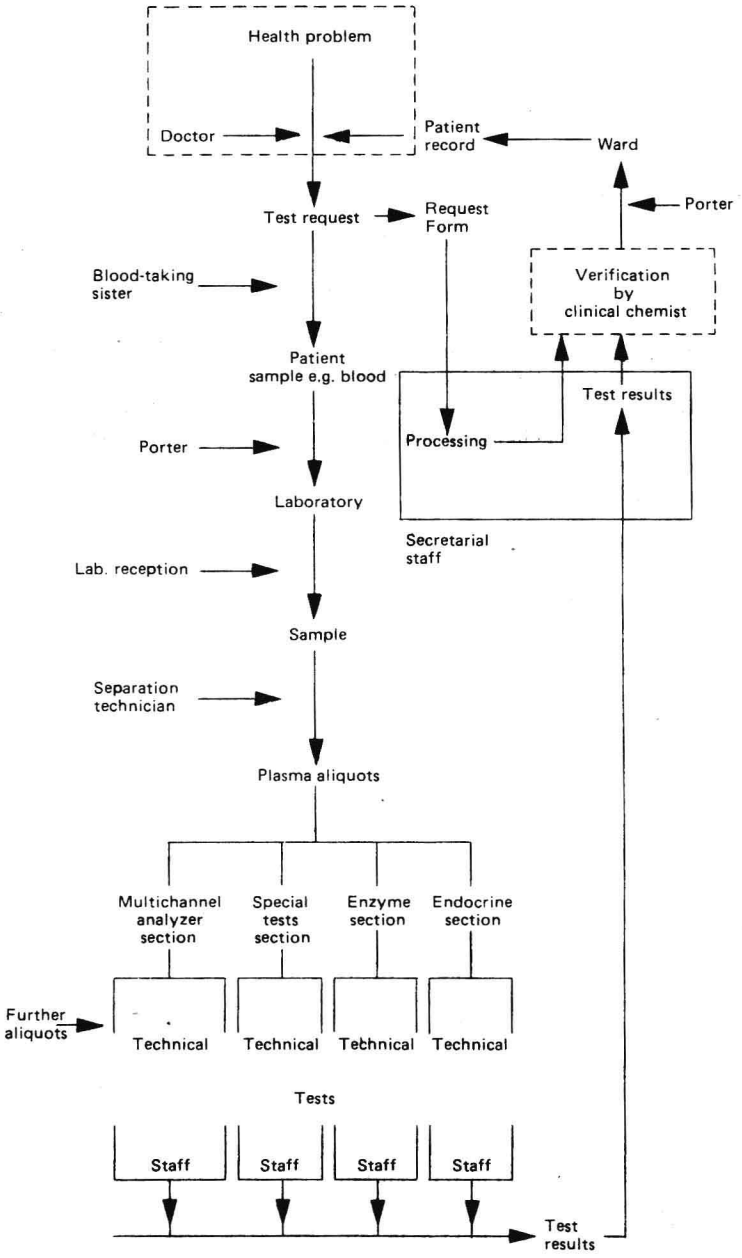


**Fig. 1.2** A typical organization of an average size clinical chemistry laboratory.

With the growing complexity of laboratory organization there is an increasing likelihood of error at each step. With a typical modern laboratory system the clinician has to assume that the sample was (1) taken from the correct patient, (2) obtained in the proper way, (3) collected in the appropriate container, (4) unadulterated, (5) kept under suitable conditions until it reached the laboratory and that the appropriate results were recorded in the case-records. In reporting the test result the clinical chemist also has to make these assumptions.

These sections of a sample's route are not under the direct control of either the doctor or clinical chemist, and so they form an 'area of uncertainty'. The areas of 'potential certainty' are those of professional trust, i.e. the clinician's assumption that the requested test has been properly performed and the clinical chemist's assumption that his laboratory has been informed of all the factors that may deflect the test result from the true one.

To effectively monitor the 'area of uncertainty' it is necessary for both doctor and clinical chemist to be able to identify both gross and subtle data disasters, but to do this the clinician has to understand some aspects of clinical chemistry and the clinical chemist has to have knowledge of some aspects of medicine.

In addition to monitoring the validity of a patient's test results, the doctor and the clinical chemist must interact at two other levels, using the relevant knowledge of each other's profession to (1) interpret the results in the light of current biochemical and medical knowledge and (2) use new knowledge to improve the diagnosis and treatment of patients.

The following sections outline the minimum of analytical and statistical knowledge that both assists in identifying errors and aids in the meaningful interpretation of patient results.

## THE INVALID RESULT

An incorrect test result can be due to many factors, including:

*Sample handling errors* (1) Sample taken from wrong patient, (2) sample switched for another during manipulations, (3) incorrect report.

*Incorrect patient preparation* (1) Posture/physical activity, (2) stress, (3) drugs/therapy, (4) biological rhythms, (5) food/alcohol.

*Sample errors* (1) Incorrect storage, (2) effect of sampling, e.g. tourniquet, haemolysis, (3) contamination, e.g. IV therapy, (4) preservation, e.g. incorrect container, (5) interference, e.g. lipaemia.

*Example* A 72 year old man making a good recovery after surgery for fractured neck of femur.

| Date | | 15/08 | 16/08 | 17/08 | 17/08* | | |
|---|---|---|---|---|---|---|---|
| Plasma | Na | 140 | 142 | 137 | 141 | mmol/l | (132–144) |
| | K | 4.2 | 3.6 | 4.0 | 3.7 | mmol/l | (3.1–4.8) |
| | Cl | 103 | 101 | 95 | 101 | mmol/l | (93–108) |
| | $HCO_3$ | 27 | 32 | 29 | 28 | mmol/l | (21–32) |
| | Urea | 12.0 | 10.4 | 14.7 | 9.6 | mmol/l | (3.0–8.0) |
| | Creat. | 0.16 | 0.12 | 0.59 | 0.11 | mmol/l | (0.06–0.12) |

The creatinine result of 17/08 appeared incompatible with the previous results and the clinical picture. A repeat specimen was therefore requested and analysed.*

Many clinical chemistry laboratories have a system whereby all results are scrutinized before they are reported to the clinical staff. Obvious handling errors involving the switching of patient samples are easily detected before reporting, particularly if a cumulative patient record system is used which allows the new results to be easily compared with previous ones obtained for the patient. The above type of error is difficult to detect when the incorrect sample is also the first sample received from the patient. In this situation, the chances of detection are much improved if the clinician provides the laboratory with clinical information that is relevant to the tests requested.

*Example* Admission samples on a 61 year old man (patient A) and a 46 year old man (patient B).

| | | Patient A | Patient B | | |
|---|---|---|---|---|---|
| Plasma | Na | 139 | 139 | mmol/l | (132–144) |
| | K | 3.7 | 3.7 | mmol/l | (3.1–4.8) |
| | Cl | 98 | 103 | mmol/l | (93–108) |
| | $HCO_3$ | 25 | 28 | mmol/l | (21–32) |
| | Urea | 17.3 | 4.8 | mmol/l | (3.0–8.0) |
| | Creat. | 0.58 | 0.09 | mmol/l | (0.06–0.12) |
| | CK | 347 | | U/l | (30–140) |
| | HBD | 360 | | U/l | (125–250) |

Since there is no comparative set of data for either patient the above results would be reported. However, this is less likely if the laboratory is able to relate the results to the 'relevant' clinical information that prompted the test requests, i.e. patient A was

admitted with chest pain and patient B was a new transfer patient with chronic renal failure, for dialysis.

With the appropriate clinical information the clinical chemist should realize that the renal function results for patient B are improbable and withhold the result. Following this, a simple investigation would reveal that plasma aliquots for patients A and B were switched prior to electrolyte and urea analysis; the enzyme results were valid for patient A.

The above types of error always carry potential danger for the patient if clinical action is taken on invalid results. Such mistakes can be minimized if test requests are accompanied by relevant clinical information. For this remedy to be effective the clinical chemist must have a clear understanding of the effect of disease and its treatment on biochemical parameters.

## INCORRECT PATIENT PREPARATION

A 23 year old woman, 32 weeks pregnant, had an oral glucose tolerance test performed to investigate the possibility of gestational diabetes.

| Time | | 09.10 | 09.45 | 10.15 | 10.45 | 11.15 | |
|---|---|---|---|---|---|---|---|
| Plasma | Glu. | 3.7 | 6.3 | 7.6 | 6.4 | 4.3 | mmol/l |
| Urine | Glu. | <0.1 | <0.1 | <0.1 | <0.1 | <0.1 | % |
| Ketones | | ++ | | +++ | | − | |

The patient was fasted for 16 hours prior to the test, causing increased fat metabolism, resulting in ketonuria. There is, therefore, no diagnostic value in requesting the urinary ketone test under these conditions. Other tests, such as lipid studies, do require an overnight fast if the results are to be diagnostically helpful. Therefore it is worthwhile to check on the requirements of patient preparation before embarking on unfamiliar tests.

## DRUG EFFECT ON PHYSIOLOGY

A 27 year old woman being investigated for anxiety and intermittent tachycardia.

| | | | | |
|---|---|---|---|---|
| Plasma | $T_4$ | 176 | nmol/l | (60–160) |
| | FTI | 141 | units | (50–150) |
| | $T_3$ | 3.4 | nmol/l | (1.2–2.8) |

Many drugs have physiological effects that are reflected in altered biochemical tests. The above euthyroid patient was taking

an oral contraceptive, the oestrogen content of which increased the plasma thyroid hormone levels by stimulating increased liver synthesis of the thyroid hormone transport protein (Chapter 20). The requesting doctor was unaware of this effect and the laboratory was unaware of the patient's drug history, resulting in the patient being referred to an endocrine clinic. Recent literature lists approximately 100 different effects that oral contraceptives can have on laboratory tests. Many other drugs can also have physiological or analytical effects on diagnostic tests. It is, therefore, important to include the patient's current drug history with the test request, as can also be seen in the following examples.

### DRUG EFFECT ON A TEST

A 61 year old woman was admitted to hospital with a provisional diagnosis of Addison's disease. A blood sample for plasma electrolytes and cortisol was taken and the patient was admitted for a full work-up (12/10). An adrenal cortex stimulation test was performed the following day (only basal level shown).

| Date | | 12/10 | 13/10 | | |
|---|---|---|---|---|---|
| Plasma | Na | 115 | 115 | mmol/l | (132–144) |
| | K | 7.2 | 7.1 | mmol/l | (3.1–4.8) |
| | Cl | 85 | 90 | mmol/l | (93–108) |
| | $HCO_3$ | 20 | 14 | mmol/l | (21–32) |
| | Urea | 12.0 | 11.3 | mmol/l | (3.0–8.0) |
| | Creat. | 0.11 | 0.09 | mmol/l | (0.06–0.12) |
| | Cort. | 97 | 869 | nmol/l | (140–690) |

The plasma electrolyte and cortisol levels in the admission sample would support the provisional diagnosis, however the basal level cortisol prior to synacthen stimulation (13/10) would not. Investigation of the marked discrepancy revealed that the patient had been given prednisolone to provide steroid cover following admission. Predniso'one behaves virtually as cortisol in the assay used by the clinical chemistry laboratory. The synacthen test therefore had to be repeated.

### DRUG EFFECT ON PHYSIOLOGY

An 11 year old boy. The clinical note accompanying the request for thyroid function studies stated: 'obese, mentally slow.'

| Plasma | $T_4$ | $<10$ | nmol/l |
|---|---|---|---|
| | TSH | $<2.5$ | mU/l |

The low $T_4$ and TSH led the clinical chemist to suggest on the patient report that the results suggested hypothyroidism secondary to anterior pituitary or hypothalamic disease. Laboratory concern at the lack of repeat or confirmatory tests led to the discovery that the patient was being prescribed $T_3$ for his obesity; the effect of $T_3$, in sufficient amounts, is to suppress both $T_4$ and TSH secretion.

## INCORRECT STORAGE

A 62 year old lady attended the renal clinic as an outpatient. A blood sample was taken, stored at + 5°C in a refrigerator overnight and sent to the laboratory in the morning for separation and analysis.

| | | | | |
|---|---|---|---|---|
| Plasma | Na | 145 | mmol/l | (132–144) |
| | K | 7.6 | mmol/l | (3.1–4.8) |
| | Cl | 98 | mmol/l | (93–108) |
| | $HCO_3$ | 25 | mmol/l | (21–32) |
| | Urea | 8.3 | mmol/l | (3.0–8.0) |
| | Creat. | 0.23 | mmol/l | (0.06–0.12) |
| | Ca | 2.41 | mmol/l | (2.15–2.55) |
| | $PO_4$ | 5.00 | mmol/l | (0.60–1.25) |
| | TP | 72 | g/l | (60–85) |
| | Alb. | 41 | g/l | (37–52) |
| | AP | 57 | U/l | (25–120) |

Prolonged contact between plasma and the red cells allows increased leakage of potassium and phosphate from the erythrocytes. Thus plasma [$K^+$] can be markedly high without any visible evidence of haemolysis. Obviously storage times that are shorter than the above case can lead to more subtle alterations.

## SAMPLE CONTAMINATION

A 76 year old woman was admitted to hospital. A blood sample was taken after an IV saline drip had been set up.

| Time | | 20.00 | 21.45 | | |
|---|---|---|---|---|---|
| Plasma | Na | 148 | 140 | mmol/l | (132–144) |
| | K | 1.0 | 2.8 | mmol/l | (3.1–4.8) |
| | Cl | 125 | 88 | mmol/l | (93–108) |
| | $HCO_3$ | 16 | 35 | mmol/l | (21–32) |
| | Urea | 4.5 | 10.5 | mmol/l | (3.0–8.0) |
| | Creat. | 0.05 | 0.13 | mmol/l | (0.06–0.12) |