SECTION 29 Biochemistry in medicine Section editor

29.1 The use of biochemical analysis for diagnosis

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ESSENTIALS Biochemistry, biochemical testing, and specialist biochemical practitioners have an important role in clinical practice in both diagnosis and

management, as emphasized by the fact that some discussion of biochemical testing appears in almost every chapter of this book. Included in this chapter are (1) a listing of the reference intervals (formerly termed reference ranges) for the most widely used biochem- ical tests, with conversion factors included (where appropriate)

to convert intervals from SI to conventional units, and their grouping into organ system profiles in common usage; (2) a description of the pitfalls and limitations of interpretation of reference intervals; and (3) some commonly used protocols for dynamic function tests. Introduction The importance of biochemical tests in modern medicine can be

seen from the fact that nearly every chapter of this book refers to the use of tests for screening, diagnosis, prognosis, monitoring progres- sion, judging the response to treatment, and measurement of drug concentrations in various fluids. This chapter discusses how laboratory tests can be used in these ways, lists

reference intervals for the commonest biochemical tests, and gives some commonly used protocols for dynamic function tests. The development of clinical biochemistry Clinical biochemistry developed as a distinct branch of pathology in the 1950s and 1960s. The increase in the use of biochemistry in clinical medicine was based on the

advances in knowledge in basic biochemistry in the first third of the twentieth century, when pains- taking research led to the discovery of how many biochemical pro- cesses worked, including energy metabolism (e.g. the tricarboxylic acid cycle), lipid metabolism, acid–base balance, the genetic code, how proteins were built and metabolized,

and how organs func- tion (e.g. the kidneys and the liver). In parallel with these basic science developments, the ability to measure molecules rapidly in small volumes of serum or plasma was a major breakthrough, first in chemical instruments such as the AutoAnalyzer, which allowed measurement of many analytes in large numbers, and then im-

munoassays, particularly labelled immunoassays, which enabled rapid measurement of analytes at very low concentrations, and led to the explosion in fields such as endocrinology. Why are tests done? Tests might be performed for a number of reasons. Diagnosis A test might be done to establish or exclude a diagnosis. Some tests are very

powerful, and can be all that is needed to establish the diag- nosis; for instance, a very high level of thyroid-stimulating hormone might be enough to say that a patient has hypothyroidism even in the absence of strong clinical features. Other tests are used to confirm or exclude a diagnosis that the clinician is considering. In this case, the

clinician has an idea of how likely a given diagnosis is (the prior probability), and seeks to increase or decrease the likelihood (the posterior probability) by using one or more tests. This is referred to as a Bayesian approach, named after Reverend Thomas Bayes. In this case, the probability of the condition given the test result is equal to the

probability of the test result given the condition multiplied by the probability of the condition divided by the probability of the test result. In formula terms: p disease test result p test result disease p disease p te (|) (|) (

× ( ) st result) . Prognosis, monitoring of disease, response to treatment, and diagnosis of complications Most testing falls into this category, and examples include meas- urement of tumour markers at the time of diagnosis and then in follow-up of the patient, and chronic disease markers such as glycated haemoglobin in diabetes. In diabetes, monitoring of urine albumin:creatinine ratios is used to detect renal complications of diabetes. 29.1 The use of biochemical analysis for diagnosis and management Brian Shine and Nishan Guha

Section 29 Biochemistry in medicine 6578 Screening The purpose of screening is to detect disease before it is clinically apparent. A screening test should target a condition that causes a significant burden where early detection and treatment lead to a suc- cessful outcome. The test needs to distinguish between affected and unaffected people, and to be acceptable to the people undergoing it. Reference intervals The reference interval (often referred to as the reference range or normal range) defines the values that we expect to find in a ‘normal’ population. It might be quite difficult to obtain specimens from a suf- ficiently large group of people who could be

considered to be free of disease, especially for analytes where there is a significant differ- ence between people of different ages or between males and females. Several big studies have included collection of specimens for defining reference intervals, including the NHANES (National Health and Nutrition Examination Survey) study in the United States of America for adults and the CALIPER (Canadian Laboratory Initiative on Paediatric Reference Intervals) project in Canada for children. Even with improved harmonization between manufacturers, and defined calibration standards, there can be big differences between the values obtained using different manufacturers' equipment, so reference intervals may not be transferable. What is worse is that the differences between methods might not be uniform or propor- tionate throughout the range of values, so a simple transformation between one method and another may not be practicable. Although this problem has been addressed for some analytes, for instance, cre- atinine, with calibration traceable to a reference standard based on isotope dilution mass spectrometry, for many other analytes, for in- stance, tumour markers, this is not yet a reality. A further problem is that many analytes vary according to the time of day (e.g. cortisol), the fed or fasted state (e.g. glucose, phos- phate), and the point in the female menstrual cycle (e.g. luteinizing hormone, progesterone), and so the reference interval must often be specified as pertaining to a particular time of the day or menstrual cycle, or there must be several defined sets of conditions for which it is given. The most common definitions for reference intervals are the cen- tral or the lower 95% of values. For normally distributed analytes, this could be defined as the mean plus or minus 1.96 standard devi- ations, but many analytes do not have a normal distribution. Many have an approximately log-normal distribution, so it may be pos- sible to derive values using a transformation. For some others, the underlying distribution can be more complex, though it can often be approximated using a Box–Cox transformation. Where this is not possible, it might be necessary to use nonparametric methods, such as the central or lower 95% of values. These methods tend to be ro- bust and to give similar values to parametric values, where the latter can be applied. An advantage of this approach is that the reference interval is less susceptible to the effect of outliers. One reason for using the word 'reference' rather than 'normal' interval is that a value within the reference interval does not ne- cessarily mean that the person is free of disease, since there can be considerable overlap between the values obtained in 'normal' and 'abnormal' people (see later in chapter). Characteristics of tests The most important characteristics of a test are its accuracy, preci- sion, sensitivity, and specificity. We can use these to show the likely behaviour of the test in diagnosis or monitoring, through the re- ceiver operator characteristic (ROC) curve, and the positive and negative predictive values. Accuracy Accuracy is how close the result is to the 'real' result. When a test for an analyte is developed, there is usually an attempt to define exactly what is being measured, and to develop tests that measure only that substance. In the case of a simple molecule such as glucose, with a well-defined molecular structure, this can be easy to define, whereas for a substance that can exist in many different forms, and may undergo post-translational modifications, such as growth hormone, this might be much more difficult. Precision Precision (or perhaps, better, imprecision) is an expression of the variability of results. Another term is 'uncertainty of measurement'. Causes of variation include: • variation within the person undergoing the test (e.g. diurnal or seasonal variations, lying and standing, and fasting versus non-fasting) • factors concerning how the specimen is taken (e.g. a blood specimen taken with or without a tourniquet) • storage until analysis (e.g. temperature, transport in an air tube system, and presence and type of anticoagulant) • variations in the measurement conditions (e.g. the measurement temperature, and variability in the amount of specimen and react- ants added to the reaction tube). The total

measurement variance is the sum of the variances in all the factors mentioned, and can be summarized as the coeffi- cient of variation (imprecision divided by the value expressed as a percentage). For example, the day-to-day variation in total cholesterol meas- urements within a person is roughly 5%. If the imprecision of measurement of cholesterol is also 5%, the total variability in meas- urement will be the square root of 52 + 52 = 7%. Sensitivity and specificity A sensitive test will be positive in all people with the condition, while a specific test will be negative in all people without the condition. The distribution of results among those with and without the condition of interest is determined by several factors. With a powerful test, capable of distinguishing those with and without the condition, the distribution is so different that everyone with the condition will have a ‘positive’ result, that is, his/her result will al- ways be distinguishable from any value that would be obtained in a person without the condition. In these conditions, the test will distinguish perfectly between people with and without the con- dition. For a test yielding a numerical result, we could thus de- fine a cut-off value that would classify all people correctly. Thus, all people with the condition would have a ‘positive’ result, and we say that the test has perfect sensitivity. Likewise, all people without

29.1 The use of biochemical analysis for diagnosis and management 6579 the condition would have a ‘negative’ result, and we say the test has perfect specificity. In most cases, however, the test will not be

optimal in this way, and so some people with the condition will have a result that could be obtained in someone without the condition, and vice versa. Whatever cut-off value we choose, some people with disease will have a negative result (false negative) and some people without the condition will have a (false-) positive result. Depending

upon our needs, and the cost of a false-positive or false-negative result, we choose an appropriate cut-off. The receiver operator characteristic curve We can summarize this dilemma by drawing a graph of the true-positive rate against the false-positive rate. The top right corner of the graph represents the situation where everyone has a

positive re- sult, that is, we choose the cut-off value so that everyone has a posi- tive result. The bottom left corner is where everyone has a negative result. For a perfect test, we would have only one point, at the top left corner, where everyone with the condition has a positive test and nobody without the disease does. For most tests, the curve will

lie above the 45° line, which indicates the situation where the result is generated by a random process. We choose the cut-off based on the cost of a missed diagnosis versus the cost of mislabelling someone as has having the condition. Figure 29.1.1 shows how the distribution curves can vary for normally distributed values, with four groups, with different means

(0, 2, 4, and 6 units) but the same standard deviation (1 unit). Even though the means between the two curves on the left differ by twice the standard deviation, there is still quite a bit of overlap between them. When these are translated into a ROC curve (Fig. 29.1.2), a value that gives a sensitivity of 90% will give a false-positive rate

of about 25%. Positive and negative predictive values

Another way of looking at the results of tests is to calculate the positive and negative predictive values. These answer the questions: ‘Given a positive/negative test, what is the probability that my patient does/does not have the condition of interest?’ The answer to this question

depends not only on the per formance of the test (sensitivity and specificity) but also on the prevalence of the condition within the population being considered. Suppose that a given condition has a prevalence of 1%, and that a test for the condition has 95% sensitivity and 95% specificity. If we consider testing 100 000 people in

the population, we can cast the results in a 2×2 table as shown. Disease Positive test Negative test Total + 950 50 1000 − 4950 94 050 99 000 Total 5900 94 100 100 000 This shows us that the positive predictive value of the test would be: 950 5900 16

% and the negative predictive value would be: 94050 94100 99 9

. %. 0.0 0.1 0.2 0.3 0.4 0 5 Value Density Group N(2, 1) N(4, 1) N(6, 1) normal Fig. 29.1.1 Examples of normally distributed data to show the overlap between the distributions with means of 0 (‘normal’ or ‘reference’ group) and 2, 4 and 6, each with standard deviation 1. 0.00 0.25 0.50 0.75 1.00 0.00 0.25 0.50 0.75 1.00 False positive True positive Group N(2, 1) N(4, 1) N(6, 1) Fig. 29.1.2 Receiver operator characteristic (ROC) curves for the ‘reference’ group compared with the other groups with means of 2, 4 and 6. The x-axis shows the false-positive rate (1 − specificity) for the ‘reference’ group, while the y-axis shows the true-positive rate (sensitivity) for the ‘abnormal’ group.

Section 29 Biochemistry in medicine 6580 However, if the prevalence of the condition is 1 in 1000, the table now looks like this: Disease Positive test Negative test Total + 95 5 100 − 4995 94 905 99 900 Total 5090 94 910 100 000 This shows us that the

positive predictive value of the test would be: 95 5090 1 9 = . % while the negative predictive value would be: 94905 95910 99 99

. %. This shows us that the positive and negative predictive values de- pend upon the prevalence of the condition. In the first example, about 84% of positive results will be found in people without the

condition, but this is about 98% in the second example.

Pre- and post-test odds The ratio of an event happening to not happening is the odds. Thus, in the earlier examples, where the prevalence (likelihood, probability) of the condition is 1%, the odds are 1:99. The relationship between likelihood and odds is thus:

odds likelihood likelihood

− 1 . Following on from this, we use tests to change the odds or the likeli- hood that the patient has a given condition. The relationship between the pre- and post-test odds can be calculated as follows: p positive with disease p positive disease p disease se

( ) ( ) ( )

×

| nsitivity p disease × ( ) p positive without disease p positive no disease p no dis

( ) ( )

× | ease specificity p no disease ( ) ( ) ( )

− ×

1 . Therefore the post-test odds are: TP FP disease no disease sensitivity

× − 1 specificity = ( ) × − pre test odds sensitivity specificity

1 . The expression sensitivity specificity /1− is also called the likeli- hood ratio for a positive result, while 1−sensitivity specificity / is the likelihood ratio (LR) for a negative result. We can thus reframe the earlier expressions as: ( ) ( ) ( ). post test odds pre test odds LR −

− × + In the first example above, the pre-test odds of the patient having the condition are 1 99 : . The post-test odds that someone with a positive test has the condition are: 1 99 0 95 0 05 1 5 2 : . . : . ×

while the odds of not having the condition given a negative test are 1 99 0 05 0 95 1 1881 : . . : . ×

In the second example, the pre-test odds are 1:999, so the post-test odds are 1 999 0 95 0 05 1 52 : . . : ×

for a positive test, and 1 999 0 05 0 95 1 18 981 : . . : ×

for a negative test. In summary To use tests effectively, the clinician should be clear what the clinical question is and how the result will help to answer this. Information that he/she needs includes the following:

1. Is the test is to rule out or rule in a diagnosis?
2. What is the prevalence of the condition in the patient population?
3. What are the specificity and sensitivity of the test?
4. What is the variation in a test that is used to monitor treatment or disease progression?
5. How likely is this test to vary between hospitals? Only when taking account of these issues can the test result be in- terpreted sensibly. It is always important to liaise with the laboratory staff if there is uncertainty about the interpretation of test results. See Tables 29.1.1–29.1.11 for reference intervals for the most widely used biochemical tests (the reference intervals given here are established for laboratory investigations available at National Health Service (NHS) hospitals in the United Kingdom, most of them from Oxford University Hospitals NHS Foundation Trust. Throughout the tables, intervals are given in Système International d'Unités (SI) and 'conventional' units together, wherever possible, with the factor for conversion from SI to conventional).

29.1 The use of biochemical analysis for diagnosis and management 6581 Table 29.1.1 Routine tests (adult) Determination Sample SI units Conversion factor (SI to conventional) Conventional units Alcohol legal limit (UK) P/S <17.4 mmol/litre × 46 <800 mg/litre Albumin P/S 32–50 g/litre × 0.1 3.2–5.0 g/dl Ammonia P 0–40 µmol/litre × 1.4 0–56 µg/dl Bilirubin P/S <21 µmol/litre × 0.058 <1.21 mg/dl Bicarbonate P/S 23–31 mmol/litre × 1 23–31 mEq/litre Calcium Ionized P/S 1.0–1.25

mmol/litre × 4.0 4.0–5.0 mg/dl Adjusted P/S 2.20–2.60 mmol/litre × 4.0 8.8–10.4 mg/dl Chloride P/S 95–105 mmol/litre × 1 95–105 mEq/litre Creatinine P/S 49–104 µmol/litre × 0.011 0.54–1.14 mg/dl Cystatin C P/S 0.5–3.4 mg/litre × 1 0.5–3.4 mg/litre eGFRa Normal GFR P/S

> 90 ml/min/1.73m2 Stage 1 CKD P/S 90 ml/min/1.73m2 (Urine findings or structural abnormalities or genetic trait point to kidney disease) Stage 2 CKD P/S 60–89 ml/min/1.73m2 (Other findings as for stage 1 point to kidney disease) Stage 3A CKD P/S 45–59 ml/min/1.73m2 Stage 3B CKD P/S 30–44 ml/min/1.73m2 Stage 4 CKD P/S 15–29 ml/min/1.73m2 Stage 5 CKD P/S <15 ml/min/1.73m2 (Or on dialysis) Ferritin S 23–674 pmol/litre × 0.445 10–300 µg/litre Glucose (fasting)b P <6.1 mmol/litre × 18 <110 mg/dl Glycated haemoglobin (HbA1C) (DCCT)i B <6.0% % × 1 <6.0 % % HbA1c (IFCC) B <42 mmol/mol Hb × 1 <42 mmol/mol Hb Iron S 11–31 µmol/litre × 5.59 61–173 µg/dl Transferrin saturation S 16–50% % 16–50% % Lactateb P/S 0.5–2.0 mmol/litre × 9.0 4.5–18 mg/dl CSF 1.1–2.4 mmol/litre × 9.0 10–22 mg/dl Magnesium P/S 0.7–1.0 mmol/litre × 2.0 1.4–2.0 mEq/litre Osmolality P/S 278–295 mosmol/kg × 1 278–295 mosmol/kg Phosphate (inorganic)c P/S 0.7–1.45 mmol/litre × 3.1 2.17–4.50 mg/dl Potassiumc P/S 3.5–5.0 mmol/litre × 1 3.5–5.0 mEq/litre Protein (total) P/S 60–80 g/litre × 0.1 6.0–8.0 g/dl CSF <0.4 g/litre × 1 <0.4 g/litre Sodium P/S 135–145 mmol/litre × 1 135–145 mEq/litre Troponin I S <5 ng/litre × 1 <5 ng/litre Troponin T S <10 ng/litre × 1 <10 ng/litre Urea P/S 3.0–9.2 mmol/litre × 2.8 8.4–25.8 mg/dl Uric acid (male) P/S 210–420 µmol/litre × 0.0169 3.5–7.1 mg/dl Uric acid (female) P/S 150–350 µmol/litre × 0.0169 2.5–5.9 mg/dl B, whole blood; CSF, cerebrospinal fluid; F, female; M, male; P, plasma; S, serum; U, urine. a eGFR (estimated glomerular filtration rate) calculated according to four-variable MDRD equation; chronic kidney disease (CKD) as defined by UK guidelines for the management of CKD. b Collection tube must contain inhibitor of glycolysis (e.g. fluoride oxalate). c Avoid delayed separation and conditions inducing haemolysis (e.g. temperature extremes).

Section 29 Biochemistry in medicine 6582 Table 29.1.2 Diagnostic enzymes Enzyme Sample Reference intervals Alkaline phosphatase P/S 30–130 U/litre Alanine transaminase (ALT) P/S 10–45 U/litre Amylase P/S 25–125 U/litre Angiotensin-converting enzyme (ACE) S 18–55 U/litre Aspartate transaminase (AST) P/S 15–42 U/litre Creatine kinase (CK) M P/S 30–200 U/litre F P/S 29–168 U/litre γ-Glutamyl transferase (γGT) P/S 15–40 U/litre Lactate dehydrogenase (LDH) P/S 90–255 U/litre F, female; M, male; P, plasma; S, serum. Table 29.1.3 Organ system profiles: commonly used profiles Organ/system Plasma/serum unless indicated Function or process dysfunction demonstrated by test Liver Albumin Estimate of protein synthesis (long half-life limits used as marker of nutritional state) Alkaline phosphatase (ALP) Bile duct membrane transport and enzyme synthesis Alanine transaminase (ALT) Hepatocellular damage Bilirubin Haemoglobin metabolism and bile duct integrity γ-Glutamyl transferase (γGT) Bile duct membrane transport and enzyme synthesis Total protein Estimate of protein (albumin and globulin) synthesis Other liver ‘function’ tests Aspartate transaminase (AST) Hepatocellular damage (less specificity than ALT) Bile acids Hepatic blood flow and bile acid clearance Prothrombin time Clotting factor synthesis Bone Alkaline phosphatase

Osteoblast activity (total activity and thus relatively poor organ specificity) Calcium Calcium homeostasis Phosphate Phosphate homeostasis Albumin For adjustment of total calcium to estimate ionized calcium Other bone ‘markers’ Bone-specific alkaline phosphatase (BALP) Osteoblast activity (tissue specific, bone formation) Calcium (urine) Calcium homeostasis N-Telopeptide (urine) (NTX) Bone resorption C-Telopeptide (CTX) Bone resorption Procollagen 1N peptide (P1NP) Bone formation Parathyroid hormone (PTH) Endocrine control of calcium homeostasis Vitamin D Endocrine control of calcium homeostasis Kidney Creatinine Glomerular filtration rate (see eGFR in Table 29.1.1) Potassium Renal tubular function Sodium Renal tubular function Urea Glomerular filtration rate Cystatin C Glomerular filtration rate Other kidney ‘function’ tests Urine pH Renal tubular function/hydrogen handling Albumin and albumin/creatinine (urine) Glomerular membrane integrity Amino acids (urine) Proximal renal tubular function Anion gap (serum and urine) Renal tubular function/acidosis Bicarbonate Renal tubular function Chloride (serum and urine) Renal tubular function

29.1 The use of biochemical analysis for diagnosis and management 6583 Organ/system Plasma/serum unless indicated Function or process dysfunction demonstrated by test Glucose (urine) Renal tubular function Electrolytes (urine) Renal electrolyte reabsorption/function Osmolality (serum and urine) Water reabsorption/concentrating ability Phosphate (serum and urine) Proximal renal tubular function Protein and protein/creatinine (urine) Glomerular membrane integrity Retinol binding protein (urine) (RBP) Renal tubular function Cardiac Brain natriuretic peptide (BNP) Amino-terminal proBNP (NT-proBNP) Raised in heart failure Creatine kinase (MB isoenzyme) (CKMB) Ischaemia: relatively poor cardiac specificity Myoglobin Ischaemia: early but poor cardiac specificity Troponin (I or T) Ischaemia/injury: good cardiac specificity and good sensitivity Skeletal muscle Aspartate transaminase (AST) Muscle damage/inflammation/ischaemia: poor specificity Creatine kinase (CK) Muscle damage/inflammation/ischaemia Table 29.1.3 Continued Table 29.1.4 Blood gases SI units Conversion factor
(SI to conventional) Conventional units Anion gap 10–20 mmol/litre × 1 10–20 mEq/litre (Na+ + K+) − (HCO3 – + Cl–) Arterial CO2 (Paco2) 4.3–6.4 kPa × 7.52 32–48 mmHg Arterial oxygen (Pao2) 11.0–14.4 kPa × 7.52 83–108 mmHg H+ ion activity 36–44 nmol/litre × 1 36–44 nmol/litre Arterial pH 7.35–7.45 pH units × 1 7.35–7.45 pH units Bicarbonate Arterial—whole blood 19–26 mmol/litre × 1 19–26 mEq/litre Venous—plasma 22–28 mmol/litre × 1 22–28 mEq/litre Base excess ±2 mmol/litre × 1 ±2 mEq/litre Table 29.1.5 Hormones Sample SI units Conversion factor
(SI to conventional) Conventional units ACTH P <10 pmol/litre × 4.55 <46 ng/litre Adrenaline (epinephrine)a, b P <0.8 nmol/litre × 183 <146 pg/ml Adrenaline (epinephrine)c U <100 nmol/24 h × 0.183 <18.3 µg/24 h Aldosterone P <200 pmol/litre × 0.03 <6 ng/dl Amino-terminal pro-brain natriuretic peptide (NT-proBNP) P <47 pmol/litre × 3.45 <400 ng/litre Brain natriuretic peptide (BNP) P <29 pmol/litre × 3.45 <100 ng/litre Cortisola 09.00 h

> 400 nmol/litre × 0.036 14 µg/dl Free U <135 nmol/24 h × 0.036 <5 µg/24 h Follicle-stimulating hormone (FSH) F— premenopausal follicular/luteal phase S 1–8 U/litre × 1 1–8 mIU/ml F—ovulatory peak <20 U/litre × 1 <20 mIU/ml F—postmenopausal 30 U/litre × 1 30 mIU/ml M 1–12 U/litre × 1 1–12 mIU/ml (continued)

Section 29 Biochemistry in medicine 6584 Sample SI units Conversion factor (SI to conventional) Conventional units Homovanillic acid (HVA)c U <48 µmol/24 h × 0.18 <9 µg/24 h Human chorionic gonadotrophin (HCG) S <4 U/litre × 1 <4 mIU/ml Insulin (fasting) S <100 pmol/litre × 0.15 <15 µU/ml Insulin-like growth factor-1 (IGF-1) S 18–60 nmol/litre × 7.6 130–450 ng/ml Luteinizing hormone F—premenopausal follicular/luteal S 2–12 U/litre × 1 2–12 mIU/ml F—ovulatory peak 20–90 U/litre × 1 20–90 mIU/ml F—postmenopausal

> 30 U/litre × 1 30 mIU/ml M 0.6–13 U/litre × 1 0.6–13 mIU/ml Metanephrine (metadrenaline) F U (24 h) <1.4 µmol/24 h × 0.195 <0.27 mg/24 h M U (24 h) <1.9 µmol/24 h × 0.195 <0.37 mg/24 h P <510 pmol/litre × 0.195 <99 pg/ml 3-Methoxytyramine U <2.5 µmol/24 h × 0.165 <0.41 mg/24 h P <180 pmol/litre × 0.165 <30 ng/litre Noradrenalinea, b P <5 nmol/litre × 169 <845 pg/ml Normetanephrine (normetadrenaline) U <4.5 µmol/24 h × 0.183 <0.8 ng/24 h P <1180 pmol/litre × 0.183 <216 pg/ml 17-β-Oestradiol S F—follicular phase 77–920 pmol/litre × 0.27 22–248 pg/ml F—mid-cycle <2400 pmol/litre × 0.27 <648 pg/ml F—luteal phase 77–1145 pmol/litre × 0.27 21–309 pg/ml M <160 pmol/litre × 0.27 <43 pg/ml Parathyroid hormone (PTH) (intact) P (EDTA) 1.6–7.2 pmol/litre × 4.0 6.4–28.8 mg/dl Procollagen type I amino-terminal propeptide (PINP) S 20–60 µg/litre × 1 20–60 µg/litre Procollagen type III (PIIINP) amino-terminal propeptide (PIIINP) S 1.7–4.2 µg/litre × 1 1.7–4.2 µg/litre Progesterone M S <2 nmol/litre × 0.314 <0.6 ng/ml F—postovulation 25 nmol/litre × 0.314 7.9 ng/ml F—follicular phase <2 nmol/litre × 0.314 <0.6 ng/ml 17-Hydroxyprogesterone (newborn) S 0.2–2.3 nmol/litre × 33.0 7–77 ng/dl Prolactina M S 70–410 mU/litre × 1 70–410 mU/litre F 110–560 mU/litre × 1 110–560 mU/litre Renin—random during day (depends on diuretics, salt intake, etc.) P 11–32 mIU/L × 1 11–32 mIU/L Sex-hormone binding protein (SHBG) M S 14–78 nmol/litre × 0.027 0.4–2.1 µg/dl F 34–148 nmol/litre × 0.027 0.9–4 µg/dl Testosterone M S 8–29 nmol/litre × 0.29 2.3–8.4 ng/ml F 0.5–2.6 nmol/litre × 0.29 0.2–0.8 ng/ml Thyroid-stimulating hormone P/S 0.3–4.2 mU/litre × 1 0.3–4.2 mIU/ml Free T3 (FT3) P/S 2.6–5.7 pmol/litre × 65.0 169–371 pg/dl Free T4 (FT4) P/S 9–19 pmol/litre × 0.068 0.6–1.3 ng/dl Vanillylmandelic acid (VMA)c U <35 µmol/24 h × 0.20 <7 mg/24 h P, plasma; S, serum; U, urine. a Should be collected under resting conditions. b Requires rapid separation and freezing. c Collection must be into bottles containing acid. Table 29.1.5 Continued

29.1 The use of biochemical analysis for diagnosis and management 6585 Table 29.1.6 Tumour markers Sample Reference intervals Units α-Fetoprotein (AFP) S <7 IU/ml CA 125 S <35 U/ml CA 15-3 S <32 U/ml CA 19-9 S <37 U/ml Calcitonin S <10 ng/litre Carcinoembryonic antigen (CEA) S <3 µg/litre Chromogranin A P <60 pmol/litre Chromogranin B P <150 pmol/litre Gastrin P <40 pmol/litre Glucagon P <50 pmol/litre Human chorionic gonadotrophin (HCG) S <4 IU/litre Neuron-specific enolase (NSE) S <12.5 µg/litre Pancreatic polypeptide (PP) P <300 pmol/litre Prostate-specific antigen (PSA) S <4a ng/ml S100 S <0.2 µg/litre Somatostatin P <150 pmol/litre Vasoactive intestinal polypeptide (VIP) P <30 pmol/litre P, plasma; S, serum. a Age-related reference ranges apply. Table 29.1.7 Vitamins and related tests Vitamin Sample SI units Conversion factor (SI

to conventional) Conventional units Vitamin A (retinol) S 0.84–3.6 µmol/litre × 28.6 24–103 µg/dl Vitamin B Thiamine (B1) B 50–220 nmol/litre × 0.034 1.7–7.5 µg/dl Riboflavin (B2) S 100–630 nmol/litre × 0.038 4–24 µg/dl Pyridoxine (B6) P (EDTA) 20–202 nmol/litre × 0.247 5–50 ng/ml Vitamin B12 S 132–662 nmol/litre × 1.36 180–900 ng/litre Folate S 7–45 nmol/litre × 0.442 3–20 µg/litre B (RBC) 283–1471 nmol/litre × 0.442 125–650 µg/litre Vitamin D metabolites S 25-(OH)D Severely deficient <30 nmol/litre × 0.40 <12 µg/litre Deficient 30–50 nmol/litre × 0.40 12–20 µg/litre Sufficient

> 50 nmol/litre × 0.40 20 µg/litre 1,25-(OH)2D3 42–169 pmol/litre × 0.38 16–64 pg/ml Vitamin E (α-tocopherol) S 11.6–35.5 µmol/litre × 0.043 mg/dl B, whole blood; EDTA, ethylene diamine tetra-acetic acid; P, plasma; RBC, red blood cells; S, serum.

Table 29.1.9 Trace elements and metals Sample SI units Conversion factor (SI to conventional) Conventional units Aluminiuma S <0.2 µmol/litre × 27 <5.4 µg/litre Toxic

> 7.4 µmol/litre × 27 200 µg/litre Arsenica B 0.03–0.31 µmol/litre × 7.5 2–23 µg/litre Cadmiuma Nonsmokers B 2.7–10.7 nmol/litre × 0.11 0.3–1.2 µg/litre Smokers 5.3–34.7 nmol/litre × 0.11 0.6–3.9 µg/litre Chromiuma S <10 nmol/litre × 0.025 <0.25 µg/litre U <115 nmol/24 h × 0.05 <6 µg/24 h Cobalt S 1.7–6.8 nmol/litre × 0.06 0.1–0.4 µg/litre Copper 0–6 months S 3.0–11 µmol/litre × 6.54 20–72 µg/dl 6 months–adult 11–22 µmol/litre × 6.54 72–144 µg/dl Ub 0.047–0.55 µmol/24 h × 65 3–35 µg/24 h Iron S 11–31 µmol/litre × 5.5 61–171 µg/dl Lead Environmental exposure Children B <0.5 µmol/litre × 20.5 <10 µg/dl Adults B <1.2 µmol/litre × 20.5 <25 µg/dl Industrial exposure B <2.4 µmol/litre × 20.5 <50 µg/dl Manganesea B 80–200 nmol/litre × 0.057 4.6–11.4 µg/litre S 9–24 nmol/litre × 0.057 0.5–1.3 µg/litre Mercury B <25 nmol/litre × 0.2 <5 µg/litre EMU <6 nmol/mmol creat × 2.0 <12 µg/g creat Selenium S 0.89–1.65 µmol/litre × 79 70–130 µg/litre Zinc P/S 10–18 µmol/litre × 0.065 0.7–1.2 mg/litre U 2–18 µmol/24 h × 0.065 0.1–1.2 mg/24 h B, whole blood; creat, creatinine; EMU, early-morning urine sample; P, plasma; S, serum. a Usually requires trace element-free collection tube, provided by laboratory. b 24-h collection into bottle previously washed with nitric acid. Check with local laboratory for ideal collection conditions. Table 29.1.8 Specific proteins and immunoproteins Sample Reference intervals Albumin S/P 32–50 g/litre α1-Antitrypsin S 1.1–2.1 g/litre Complement C3 S 0.70–1.90 g/litre C4 S 0.14–0.40 g/litre Caeruloplasmin S 0.15–0.60 g/litre C1 inhibitor (antigenic) S 150–350 mg/litre C1 inhibitor (functional) S 70–130 % normal reference sample C-reactive protein (CRP) S <5 mg/litre Ferritin S 10–300 µg/litre Immunoglobulins IgG S 6–13 g/litre IgA S 0.8–3.0 g/litre IgM S 0.4–2.5 g/litre Mast-cell tryptasea S 0–16 µg/litre β2-Microglobulin S <3.0 mg/litre Thyroid peroxisomal antibodies S <60 U/ml Transferrin S 1.8–3.6 g/litre P, plasma; S, serum. a For anaphylaxis, samples

within 1, 4, and 24 h after reaction.

29.1 The use of biochemical analysis for diagnosis and management 6587 Table 29.1.10 Urinary and faecal reference intervals SI units Conversion factor (SI to conventional) Conventional units Albumin M <2.5 mg/mmol creat × 12 <30 mg/g creat F <3.5 mg/mmol creat × 12 <42 mg/g creat Amylase Secretion rate <17 IU/h × 1 <17 IU/ h Clearance ratio 1–4 % × 1 1–4 % Arginine 1–6 µmol/mol creat × 1.49 1.5–9 mg/g creat Calciuma 2.5–7.5 mmol/24 h × 40 100–300 mg/24 h Chloride 110–250 mmol/24 h × 1 110–250 mEq/24 h Copperb 0.047–0.55 µmol/24 h × 6.54 3–35 µg/ 24 h Cortisol <135 nmol/24 h × 0.036 <4.9 µg/24 h Creatininec 5–18 mmol/24 h × 0.11 0.6–2.0 g/24 h Cystine 5–42 µmol/mmol creat × 2.0 10–84 mg/g creat Faecal elastase

> 200 µg/g dry weight × 1 200 µg/g dry weight Homovanillic acid (HVA)a <48 µmol/24 h × 0.18 <9 µg/24 h Hydroxyindole acetic acid (5-HIAA)a <40 µmol/24 h × 0.19 <7.6 mg/24 h Lead <0.4 µmol/litre × 200 <80 µg/litre Lysine <35 µmol/mmol creat × 1.28 <45 mg/g creat β2-Microglobulind <370 µg/24 h × 1 <370 µg/24 h Magnesium 3–5 mmol/24 h × 24.5 74–123 mg/24 h Ornithine 4–17 µmol/mmol creat × 1.1 4.4–18.7 mg/g creat Oxalatea 0.1–0.46 mmol/24 h × 9.0 0.9–4.14 mg/24h Phosphate (inorganic) 13–42 mmol/24 h × 0.03 0.4–1.3 g/24 h Porphyrins—urinee Porphobilinogen <1.5 umol/mmol creat × 1 <1.5 umol/mmol creat Total porphyrin <35 nmol/mmol creat × 1 <35 nmol/mmol creat Potassium—urinec, f 20–60 mmol/litre × 1 20–60 mEq/litre 40–120 mmol/24 h × 1 40–120 mEq/24 h Potassium—faecal ~5 mmol/24 h × 1 ~5 mEq/24 h Protein <100 mg/24 h × 1 <100 mg/24 h Sodium—urinec, f 20–125 mmol/litre × 1 20–125 mEq/litre 40–220 mmol/24 h × 1 40–220 mEq/24 h Sodium—faecal <10 mmol/24 h × 1 <10 mEq/24 h Ureac 400–700 mmol/24 h × 0.06 12–20 g/24 h Uric acidc 1.5–4.5 mmol/24 h × 0.167 0.25–0.75 g/24 h Vanillylmandelic acid (VMA)a <35 µmol/24 h × 0.20 <7 mg/24 h F, female; M, male; mmol creat, mmol of creatinine. a Collection must be into bottles containing acid. b 24-h collection into bottle previously washed with nitric acid. c Partially influenced by diet. d Must be kept alkaline. e Avoid exposure to light. f Urine electrolyte results must be interpreted in the light of concomitant serum electrolyte results. Check with local laboratory for ideal collection conditions.

Section 29 Biochemistry in medicine 6588 Table 29.1.11 Therapeutic drugs Sample SI units Conversion factor (SI to conventional) Conventional units Amikacin Trough S ≤17 µmol/litre × 0.59 ≤10 mg/litre Peak S 34–51 µmol/litre × 0.59 20–30 mg/litre Amitriptyline S 179–536 nmol/litre × 0.28 50–150 µg/litre Carbamazepine P 17–51 µmol/litre × 0.235 4–12 µg/ml Ciclosporina B 83–333 nmol/litre × 1.20 100–400 µg/litre Clozapineb P (EDTA) 1100–1890 nmol/litre × 0.318 350–600 µg/litre Digoxinb P 0.6–2.6 nmol/litre × 0.78 0.5–2.0 µg/litre Ethosuximide P 280–700 µmol/litre × 0.14 40–100 µg/litre Gentamicin Trougha S ≤4 µmol/litre × 0.48 ≤2 µg/ml Peak S 10–31 µmol/litre × 0.48 5–12 µg/ml Lamotrigine S 10–59 mmol/litre × 0.256 2.5–15.0 µg/ml Levetiracetam S 70–270 mmol/litre × 0.171 12–46 µg/ml Lithiumc—therapeutic S 0.5–0.8 mmol/litre × 1 0.5–0.8 mEq/litre

Methadone P 430–720 nmol/litre × 0.349 150–250 µg/litre Mycophenolate P 1–3 mg/litre Phenobarbital P 40–160 µmol/litre × 0.23 10–40 µg/ml Phenytoin P 21–80 µmol/litre × 0.24 5–20 µg/ml Sirolimusa B 5–20 µg/litre Tacrolimusa B 5–15 µg/litre Teicoplanina S 10–60 µg/ml Theophylline P 55–110 µmol/litre × 0.18 10–20 µg/ml Vancomycin Trougha S 7–10 µmol/litre × 1.44 10–15 µg/ml Peak S 29–58 µmol/litre × 1.44 20–40 µg/ml B, whole blood; P, plasma; S, serum. a NB: based on predose sample. b NB: therapeutic range—sample taken at least 6 h after dose. c NB: therapeutic range—sample taken at least 12 h after dose.