
Specific laboratory investigations for assessments and management of drug problems

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Much of the drug testing available today is able to determine the presence or absence of a variety of psychoactive substances in a range of body fluids and tissues. For the results of such tests to be confidently interpreted, additional information is required, including general assessment and history-taking. In a wide range of large psychiatric surveys, substance dependence emerges as one of the most common mental health-related disorders, and it is also the one that is least likely to be treated. The range of available tests can be best considered as acting to support and complement a broader assessment and diagnostic procedure.

The aim of this paper is to outline the variety of laboratory investigations available which could be considered as biological indicators of substance use and misuse. The strengths and weaknesses of different approaches and different body matrices are reviewed (urine, blood/plasma monitoring, saliva and hair testing), along with other possible materials not usually considered, with a focus on the clinical usefulness of these procedures.

A drug may be detected in any body fluid or tissue, but there are practical limitations to the extent to which samples can be and are used, and the mechanism of collection and supervision of samples are critical to the procedure.

Chain of custody

The procedure of ensuring that an identified sample was provided by a specified individual (chain of

custody), and has subsequently been correctly labelled to ensure accuracy, must be properly documented. Chain of custody procedures usually require the collection of a urine sample witnessed by a designated member of staff (clinician, nurse, drug worker, therapist, etc.), and written confirmation of its validity from the individual voiding the sample, as detailed in Box 1 (Combs & West, 1991).

Legal and ethical issues

The legal issues that have surfaced in the development of workplace drug testing programmes were reviewed by Long (1989). The legal cornerstone of

Box 1. Chain of custody procedures

Before, during and after urination, collection site personnel shall have the urine specimen in sight

Urine container shall be tightly capped and properly sealed and labelled with name and time date of collection

Approved chain of custody form shall be utilised to maintain accountability and accompany sample from initial collection to final disposition

Reliable transportation (courier system) to the laboratory is required

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drug testing is a policy agreement which usually takes the form of a contract between employers and employees and may include the points listed in Box 2 (Osterloh & Becker, 1990).

Those who oppose drug testing usually argue around issues concerned with civil rights. The courts have generally ruled that mandatory drug testing is a form of search and in some cases falls under constitutional protection. However, the potential value of testing to public health, safety and security in certain professions has led to wider legal support for testing programmes (MacDonald, 1990).

Rationale

The rationale for performing analytical tests varies depending upon the question(s) to be answered. Drug treatment services vary in the way that they practise drug screening. Services may use test results to gauge efficacy of therapy, or residential units requiring abstinence may use random checks of clients. Clinicians may also use drug tests to make the initial diagnosis of substance misuse, for screening as a requirement of a treatment programme when measuring compliance, or for screening as a useful adjunct to a full drug history to gauge drug exposure over time.

Major challenges for testing procedures include the vast array of drugs that may be consumed, the hugely different clinical and legal significance of test results (which may not always be obvious in the laboratory), and the need for specific approaches for these different substances. One of the limitations of drug testing is that it can give no indication of the presence or absence of physical dependence.

Drug testing

Selecting the biological matrix and the challenge of interpretation

The choice of body fluid is influenced by the pharmacokinetics of the drugs being tested for, and by the period of time that the clinician wishes to consider. Blood and, to a lesser degree, saliva are likely to give the most accurate measurement of drugs currently active in the system, whereas urine provides a somewhat broader time frame, but with less quantitative accuracy. Hair provides a substantially longer time frame.

Box 2. Drug testing policy agreement

The need for drug testing and why
 Conditions of testing
 Procedures for collecting specimens
 Consequences of the test result
 Availability of treatment

Routine drug testing

The standard procedure for routine analysis for drugs of misuse is an initial screening test using an automated commercial immunoassay kit such as an enzyme-mediated immunoassay (EMIT), followed by thin-layer, gas or liquid chromatography for confirmation of a specific drug in a sample (Braithwaite *et al* 1995; Simpson *et al* 1997). A confirmatory test is usually recommended (which should be qualitatively different from the first) following the initial screening test to specifically identify the compound detected because of the implications of a positive finding. Initial screening tests only identify the class of drug (i.e. opiate, benzodiazepine, etc.). The need to confirm the identity of the actual drug present will vary depending on whether this is in a legal, employment or clinical setting. The most sophisticated drug testing approach is gas chromatography coupled with mass spectrometry (GC-MS) which is currently regarded as the 'gold standard' by which to confirm the presence of a drug.

Although drug testing can be easily undertaken, there remains the problem of interpreting the results for clinical use. The picture is often complex; a drug may be present as metabolites and the parent drug may only be present in relatively low concentrations (buprenorphine, lysergic acid diethylamide (LSD) and Δ^9 -tetrahydrocannabinol) or not detected at all. Heroin (diamorphine), for instance, is seldom detected in blood as it is rapidly converted to an intermediary metabolite 6-monoacetylmorphine (MAM) and thus is not excreted into the urine.

Interpretation is also complicated by the relationship between compounds from the same drug class, which may share common metabolic end-products. For example, the benzodiazepine oxazepam, a prescription-only medication, is also a metabolic by-product of chlordiazepoxide, diazepam, clorazepam and temazepam. A similar problem exists with the opiate drugs. The principle metabolite of heroin is morphine, but morphine is also a metabolite of codeine. Consequently, the detection of MAM is generally considered to be a more specific indication

of heroin consumption. In contrast, dihydrocodeine (often confused with codeine) has its own distinct metabolic pattern. The clinical explanation of drug testing results is a challenging and often critical problem, particularly when establishing legitimate *v.* illegal use and all of its attendant complications.

False positives and false negatives

In qualitative screening tests, each sample is reported either positive or negative for a particular drug or drug group. There are four possible interpretations of the test result, as in Table 1.

The two true test results accurately reflect the clinical situation. However, a true positive on a screening test may not itself indicate the specific drug and cannot indicate the dose, time or route of drug administration. A true negative indicates that no drug was taken within the time desired for its use to be detected. Clinicians should be aware of the time taken for drugs to be eliminated from the body (see Table 2), since a negative test could result from not sampling soon enough after drug consumption. Clinically, a false negative may be defined as a negative finding in a sample from a patient known to have recently taken the drug of interest. False negatives can also occur when the threshold of sensitivity of the analytical procedure is set above the limit of detection of the drug.

Chemically, a false negative report may occur when the altered composition of a sample or endogenous components from the sample masks the presence of a drug of interest during analysis of a sample known to contain this substance. Aspirin ingestion and its presence in urine interferes with the analytical process in all EMIT assays, potentially yielding false negative results for drug screens (Linder & Valdes, 1994). In the laboratory, a false positive test result arises when the positive test report is from the analysis of a biological sample which does not contain the drug in question. It is an incorrect identification of the presence of the determined compound. If the analytical method is subject to interference from artefacts or compounds

Table 1 Interpretation of test result

	Person has taken drug	Person has not taken drug
Test result positive	True positive	False positive
Test result negative	False negative	True negative

Table 2 Approximate duration of detectability of commonly used substances and some of their metabolites in urine (based on common laboratory cut-off values)

Substance	Duration of detectability
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<i>Stimulants</i>	
Amphetamine	2–3 days
MDMA (ecstasy)	30–48 h
Methamphetamine	48 h
Cocaine ¹	6–8 h
Cocaine metabolite/ benzoylecgonine	2 days
<i>Barbiturates</i>	
Short-acting (cyclobarbitone)	24 h
Intermediate-acting (pentobarbitone)	48–72 h
Long-acting (phenobarbitone)	≥ 7 days
<i>Benzodiazepines</i>	
Short-acting (triazolam)	24 h
Intermediate-acting (temazepam, chlordiazepoxide)	40–80 h
Long-acting (diazepam, nitrazepam) ²	≥ 7 days
<i>Opiates</i>	
Methadone (maintenance dosing)	7–9 days
Codeine/morphine ³	24 h
Morphine glucuronides	48 h
Codeine glucuronides	3 days
Propoxyphene/ norpropoxyphene	6–48 h
Dihydrocodeine	24 h
Buprenorphine ⁴	48–56 h
Buprenorphine conjugates	7 days
<i>Cannabinoids (marijuana)</i>	
Single use	3 days
Moderate use	4 days
Heavy use (daily)	10 days
Chronic heavy use ⁵	≤ 36 days
<i>Other</i>	
Methaqualone	≥ 7 days
Phencyclidine (PCP)	8 days
Lisergic acid diethylamide (LSD) ⁶	24 h

1. Cocaine is rapidly converted to benzoylecgonine in alkaline urine at room temperature.
2. The presence of nordiazepam, an active metabolite of diazepam, in urine may prolong detection.
3. Morphine is rapidly oxidised at 4°C. Urine collection vessels should be filled to the top to minimise this effect.
4. Usual doses results in very low levels of these compounds in urine. Detection may be possible after very recent use.
5. The lipophilic nature of the cannabinoids may prolong detection in urine with chronic dosing (Dackis *et al*, 1982).
6. LSD is extremely photolabile and samples thought to contain this drug should be stored protected from light.

of similar structure to the drug of interest, then specificity is said to be low and this can lead to false positive results.

Clinical misinterpretations of immunoassay results (initial screening test) are a common source of false positive reporting. Immunoassays, as a measurement technique, are generally the most susceptible to interference from compounds similar to the drug in question, since they generally recognise all compounds belonging to a particular class of drug, including metabolites. An opiate-positive report using immunoassays, for instance, can be indicative of the presence of any number of opiate-type drugs and not necessarily illicit substances. Similarly, failure to acknowledge medication taken legitimately that is chemically similar to the drug of interest (e.g. pseudoephedrine in cough medicine with immunoassays for amphetamine) may lead to a false positive interpretation.

Clinically, a false interpretation of the result of a positive test can also arise because of passive drug exposure (cannabis or nicotine). Another cause of false interpretation of the result may be the presence (as already mentioned) of a compound which is actually a metabolite of other compounds. For example, the presence of morphine in urine is often assumed to be indicative of heroin use but it is important to recognise that urinary morphine may result from several sources (see Box 3). The 'poppy seed defence' has been shown to be a plausible explanation of a positive test result (as little as half a slice of poppy seed cake will give a positive immunoassay response). So much so that each case should be interpreted on its own merits and with caution (George, 1998).

Clearly, the more information that the clinician or drug worker can gather during sample collection, the better. Although self-reports of drug use have been criticised as an inaccurate source of information, carefully presented questions can produce a wealth of valuable information. Self-report interviews are all too often disregarded by workers in the field when they could be used as an important component of the screening test.

Box 3. Potential sources of urinary morphine

Consumption of codeine

Opiate drugs in foodstuffs, e.g. poppy seed strudel danish pastry (Selavka, 1991), poppy seed cake (George, 1998)

Analgesic prescription preparations, e.g. Gee's Linctus, kaolin and morphine mixture

Currently available laboratory investigations of drug use

Urine

Currently, urine is the preferred biological fluid for the screening of drugs of misuse (Wolff *et al*, 1999). Urinalysis is a well-known technology in which most of the analytical problems have been discovered and dealt with. The significant advantage of urine for drug testing is that it is generally available in sufficient quantity and the drugs or their metabolites tend to be present in relatively high concentrations (Moffat *et al*, 1986).

A variety of methodological techniques have been employed for screening urine samples, and many comparative studies have been carried out to determine the most efficient system (Wilson *et al*, 1994). Automation has enabled mass screening of urine samples by a variety of techniques. Enzyme-linked immunosorbent assay (ELISA) is potentially the most cost-effective in terms of sample turnover and can be utilised for whole blood, serum, urine, saliva and hair (Simpson *et al*, 1997).

A recent innovation has been the introduction of self-contained drug testing kits for on-site testing. These are marketed for testing for a variety of drugs in urine and are designed to provide rapid access to test results without the need for laboratory facilities (Armbruster & Krolak, 1992). Those that test for cannabis (see Jenkins *et al*, 1993, 1995) are among the most commonly used.

These tests offer advantages in terms of simplicity, ease of performance and rapid access to test results, but potential drawbacks include the subjective and qualitative nature of the kits and, in some instances, the lack of a positive control (Armbruster & Krolak, 1992). There is a paucity of data on the validity of stick tests, which are produced by some manufacturers. The main problem with most self-contained urine tests is interpretation of the results (George & Braithwaite, 1995). Detecting the colour change is a highly subjective process and difficult for the inexperienced eye. The other problem is the cost, which can be prohibitive. Test kits are best suited for testing small numbers, but are probably not suitable for widespread routine use.

It is often thought that detection times for drugs in urine will vary with drug dosage, but this is not usually the case (certainly not to any great extent) since chronic drug consumption only extends the detection time of the parent drug slightly. A three-days-per-week urinalysis schedule has been reported as the most efficient to pick up illicit cocaine or heroin use (Cone *et al*, 1992). However, the cost of

conducting such frequent tests would be prohibitive for most services and is only recommended in exceptional circumstances.

The benefits of urine for screening for drugs of misuse are well known, but it has also been widely recognised that the collection of urine for drug screening has limitations. Care should be observed by those who collect urine for drug screening. For instance, morphine is rapidly oxidised at 4°C and urine collection vessels should be filled to the top, where possible, to minimise this effect.

Drug addicts may at times attempt to influence the results of a screening test to produce either a positive (prerequisite for pharmacotherapy) or negative (implied abstinent) test result. Various methods have been reported to achieve a false negative result. Household detergents added to urine prior to drug testing also cause false negative results for amphetamine, cocaine, morphine and cannabis, respectively. Ibuprofen in urine has been associated with false negative GC-MS confirmation results for cannabis (Brunk, 1988) while sodium chloride may lead to false negative results with basic drugs such as opiates (Kim & Cerceo, 1976). Commercially available products for 'flushing' illicit substances from the body are used to achieve a negative result in a urine sample that is otherwise positive for one or more drugs (see Wu *et al*, 1994).

Other steps taken include drinking copious amounts of fluid to dilute the urine; substituting urine for weak black tea; providing a urine sample collected previously (when abstinent) or a sample from a drug-free friend; or diluting the sample by using water from a tap or the toilet (Widdop & Caldwell, 1991). To help prevent dilution of the sample at the collection site, a blue dye can be added to the water in the toilet bowl. Similarly, manipulation to achieve a false positive result has been achieved by adding drugs to the urine sample after voiding (e.g. methadone detected in the absence of its main metabolite 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP)). The best way to ensure sample validity is to witness the collection of the urine sample. This may raise several issues around infringements of a patient's personal privacy, more practical matters of staffing (i.e. female staff to observe female clients, etc.), and availability of facilities for such operations. There are, however, simple physical tests that may be taken to check the validity of a urine sample (see Table 3).

The disadvantages of using urine to test for the presence of drugs of misuse have to be weighed up against the advantages of having a fluid that requires little pre-analysis preparation and can be collected non-invasively in large volumes. Urinalysis remains the most reliable tool for identification of the presence of most illicit substances.

Table 3 Physical tests employed for collecting a valid urine specimen

Suspected manipulation	Physical test
Dilute urine sample	Measure specific gravity: normal range 1.016–1.025. Sample dilute when ≤ 1.003
Dilute urine sample	Measure creatinine level: normal range male 1.5–2.0 g/24 h female 0.8–1.5 g/24 h. Specimen dilute when creatinine < 0.2 g/dl
Substituted sample (tea/water/someone else's urine)	Check temperature is 33–37°C: measure within 4 min. of voiding
Cold sample	Check temperature is 33–37°C: measure within 4 min. of voiding
Adulterated sample (bleach, detergents, etc.)	Check pH: normal range 4.5–7.8

Blood

Blood is the most useful biological matrix for the quantitative measurement of drugs and for interpretation by comparison with previously reported blood concentrations corresponding to therapeutic, toxic and fatal conditions (Moffatt *et al*, 1986). Also, because drugs leave the blood fairly rapidly, blood is most useful for identifying very recent drug use. Therapeutic levels of drugs generally exist in blood in low concentrations, typically in the 5 ng/ml to 5 µg/ml range. Some substances are found at lower concentrations in blood, notably LSD, flunitrazepam and buprenorphine. However, there is the advantage that when misused, drug concentrations in blood may be 2–3 times higher than normal levels observed with therapeutic dosing.

Since most drugs of misuse leave the blood fairly rapidly (within a few hours of drug use), blood concentrations (e.g. cocaine and ecstasy) will have fallen below detection levels applied in routine drug screening. The elimination of a drug from blood (half-life) is determined by the physiological and chemical characteristics of the particular drug and the route by which it is administered. It usually takes 5–7 half-lives for a drug to be totally eliminated from the body (see Table 4).

Until analytical assays are available to assess the biological effects of substance misuse, or until drug receptor concentrate can be estimated to indicate potential drug response, there is an increasing need

for therapeutic drug monitoring (TDM) to predict clinical outcomes of therapeutic regimes (Flanagan, 1995). Blood collection, however, is probably the least favoured procedure for routine drug testing, and the mechanics of storage of blood samples collected for routine drug screening presents additional problems for the clinician (see Box 4).

Although clinical pharmacology is a well-established discipline, its influence on substance misuse treatment has been minimal. Dosage control has been the traditional tool for defining efficacy, safety and dose response in prescribing programmes for drug dependence. However, there is mounting evidence, particularly for methadone treatment, that a drug concentration strategy of treatment evaluation may represent a better approach to achieving optimal dosing (Wolff & Hay, 1994).

Monitoring blood levels in maintenance therapy

Therapeutic drug monitoring is the science that combines measurement of blood drug concentrations with clinical pharmacokinetics. One of the major benefits of TDM is being able to monitor compliance with pharmacotherapy. The study of patient compliance is not new, and non-compliance is recognised to be common, occurring in all kinds of medical conditions of which drug dependence is no exception. Urinalysis drug screening is an important way of assessing illicit drug use by patients during methadone treatment but, unlike TDM, sheds no light on whether a patient is taking all their medication (at the correct time and in the correct amount), or is using extra medication (obtained illicitly), or is selling some of their prescription, perhaps to other users. There is growing evidence that plasma methadone measurements can provide answers to these questions (Wolff *et al*, 1992) (see Table 5).

Box 4. Issues to be overcome for blood collection

- Requires trained personnel
- Is an invasive procedure
- Involves the attendant risk of needle-stick injury and possible transmission of either HIV or hepatitis B C virus
- Is difficult to obtain in large volumes
- Is difficult in intravenous drug users who may have thrombosed or sclerosed surface veins

Table 4 Approximate plasma elimination half-lives for drugs of misuse

Drug	Half-life (mean value)
Heroin	2 min
Morphine	3 h
Morphine glucuronides ¹	7.5 h
Dihydrocodeine	4 h
Codeine	3 h
Codeine glucuronides ¹	12 h
Buprenorphine ²	8 h
Buprenorphine glucuronides ²	24 h
Methadone ³	36 h
Amphetamine	12 h
Cocaine	1 h
Benzoylcegonine (cocaine metabolite) ⁴	7.5 h
MDMA (ecstasy)	6 h
Nitrazepam	28 h
Flunitrazepam	25 h
Temazepam	10 h
Diazepam	48 h
Nordiazepam ⁵	40–100h
Cannabis ⁶	20 h
Cannabinoid metabolites ⁷	25–28h

1. Cone *et al* (1991).

2. Hanks (1987).

3. Wolff *et al* (1997).

4. Ambre (1985).

5. Nordiazepam is an active metabolite of diazepam
Moffat *et al*, 1986).

6. Hunt & Jones (1980).

7. Lemberger *et al* (1971) and Law *et al* (1984).

Studies of methadone treatment response have shown that patients who comply with the recommended course of treatment have longer-lasting post-treatment benefits (Allison & Hubbard, 1985). Thus, it is discouraging for many practitioners that opiate addicts in treatment are frequently poorly compliant or non-compliant subjects. Dosage alterations based on interpretation of plasma measurements may help more patients to do well on methadone (Wolff *et al*, 1991a, 1997).

Hair

Human scalp hair testing is a fairly new biological tool for drug screening. The obvious advantage of hair testing is that this technique offers the potential for information over a much longer time-scale than can be obtained with blood, urine and saliva analysis. The analysis of misused substances in hair is problematic because these compounds are found in very low concentrations, usually within a range

Table 5 Indications for plasma methadone measurements include:

Decision to request plasma measurement	Interpretation
<i>Assessment of compliance with methadone</i> Monitor take home medication Monitor prescription of ampoules Suspect overprescribing (higher dose than needed) Suspect multiple scripting	<i>Subtherapeutic concentrations</i> Not taking all of dose <i>Higher than expected concentrations</i> Consuming extra methadone
<i>Methadone induction change in dosage regime</i>	<i>Subtherapeutic concentrations</i> Steady state may not have been achieved
<i>Change in clinical state of patient</i> (i.e. pregnancy)	<i>Subtherapeutic concentrations</i> Increased blood volume in third trimester may reduce drug concentration with possibility of the onset of opiate withdrawal
<i>Potential drug interaction due to change in co-medications</i>	<i>Subtherapeutic concentrations</i> Enzyme inducing drugs (rifampicin, phenobarbitone, phenytoin, carbamazepine) will cause the onset of opiate withdrawal symptoms <i>Toxic concentrations</i> Enzyme inhibiting drugs (protease inhibitors – ritonavir, isoniazid, possibly cimetidine) may cause nausea or sedation
<i>Concerns about alcohol consumption</i>	<i>Subtherapeutic concentrations</i> Bingeing with alcohol may increase clearance and cause the onset of withdrawal symptoms

of 10 pg/mg to 10 ng/mg hair. Nevertheless, most illicit substances have been detected in hair. Yet it is noticeable that there is little in the way of comprehensive drug screening methodology for this matrix.

Advocates of scalp hair analysis have emphasised the ease with which this matrix can be collected but there has been a tendency to gloss over the many technical and even practical difficulties involved (Cone, 1996). The mechanism by which a substance is deposited in hair remains unknown (Joseph *et al*, 1996), but it is likely that the amount and type of melanin is important in determining how much drug enters hair from the systemic circulation. This has led to claims that there may be a racial bias in hair analysis, but human studies to date have not confirmed this.

The physico-chemical properties of each particular substance play an important role in the incorporation of a drug into hair. Lipophilicity and basicity (alkalinity) are clearly important in the blood-to-hair route. Basic drugs (like opiates, amphetamine and cocaine) are incorporated easily into hair (Nakahara *et al*, 1995), acidic drugs (aspirin or methaqualone) much less so. Cannabis appears

to be particularly difficult to detect in human scalp hair although analytical procedures have been reported (Kintz *et al*, 1995).

Perhaps a unique problem with scalp hair analysis is passive contamination of the external surface of the hair, which presents an obvious interpretational problem. Dupont & Baumgartner (1995) demonstrated that exogenous false positives could be produced due to contamination of hair by drugs present in the environment. Decontamination of hair to exclude external interferants from analysis has become an integral step in most methodological procedures, but this process is very labour intensive and some hair types, such as thick black hair, seem more resistant to this process than others (Blank & Kidwell, 1995).

While hair collection for drug screening is non-invasive there are certain precautions to be taken into account. Marsh (1997) reports that maintaining alignment of, securing and identifying the cut ends of hair are critical if segmentation (quantification of time with drug concentration) is required. The style of hair worn is also a source of variability. Hair growing from a closely cropped head can not

possibly contain the same concentration, after the same dose of drug, as hair that has not been cut over a long period of time. Variations in the expected concentration can exceed 20% (Sachs, 1995), and it is not clear from the literature how one corrects for these discrepancies. Additionally, some patients wear wigs, and hair from other parts of the body is needed for these and for people with shaved heads.

In regular practice in the addiction field, the clinician may be better served by urinalysis (Strang *et al*, 1993). Hair analysis should be seen as an adjunct to other screening procedures, for obtaining information regarding patterns of drug use, for establishing a drug history over time, or as a research tool, for example, in investigation of passive exposure to tobacco.

Likely future development of new laboratory investigations

Saliva

Determination of drug concentrations in saliva is an exciting new territory, particularly since the collection of samples is non-invasive, and this matrix has the potential to provide both quantitative and qualitative information on the drug status of an individual under examination. Measurements of illicit drugs have been investigated in saliva for more than a decade, but early work was hampered by inconsistent collection procedures (Haeckel & Hanecke, 1996). For the moment, the role of this biological fluid as a detection and monitoring tool remains uncertain.

Sample collection time is also an important variable. For drug addicts who self-administer by

oral, intranasal and smoking routes, 'shallow depots' of drug can result, which contaminate the oral cavity (Cone, 1993). This produces elevated salivary concentrations for several hours after ingestion and, although potentially useful in cases of overdose or accidental poisoning (Wang *et al*, 1994), should be borne in mind when interpreting results for routine drug screening. The presence of tetrahydrocannabinol in saliva, for example, appears to be due primarily to contamination of the oral cavity following smoking of marijuana cigarettes. Being highly protein-bound, cannabinoids do not readily pass from blood into saliva and cannabis itself inhibits salivary excretion (Karlsson & Strom, 1988).

Saliva testing for drugs of misuse can, however, provide information on the drug status of an individual undergoing testing. Generally, once drugs have been eliminated from the buccal cavity, there is a high correlation between salivary and plasma drug concentrations for many compounds (Huestis & Cone, 1998) such as cotinine (Curvall *et al*, 1990) and methadone (Wolff *et al*, 1991*b*). Saliva for drug analysis has the advantage of being relatively easy to obtain and collection can be carried out by non-clinical personnel (Gorodischer *et al*, 1994). Commercially available tools may make possible the collection of saliva in a more standardised manner than has been possible previously. This would enable more frequent use of saliva in substance misuse treatment services, which would be particularly advantageous in intravenous drug users in whom it is often extremely difficult to find venous access. It would also enable more objective measurement and corroboration of self-reported drug use in a variety of social survey situations.

Despite the fact that drugs are detectable in saliva for a slightly shorter period than in urine, it is possible that salivary detection procedures will expand significantly in the next few years owing to the particular advantage over blood of the non-invasive nature of collection.

Breath

The analysis of human breath has been extensively used for the measurement of ethanol as a gauge of alcohol consumption (Cowan *et al*, 1996). Generally, the variety of instruments used to monitor breath are portable, economical and easy to use for patient sampling (Grote & Pawliszyn, 1997). Some drugs are naturally volatile compounds that mix freely with air, such as anaesthetic gases (e.g. nitrous oxide) and inhalants (e.g. correction fluid and solvents). Others require combustion (e.g. tobacco, marijuana and crack cocaine). Although tetrahydrocannabinol was identified in the breath of marijuana

Box 5. Additional potential uses of hair analysis

In post-mortem examination (Kintz *et al*, 1992)

Forensic cases (Moeller, 1996)

Medico-legal work in establishing a history of past exposures to therapeutic or abused substances (Huestis, 1996)

Hair samples from children may help in child protection cases by providing evidence of previous drug exposure (Lewis *et al*, 1997)

Neonatal hair analysis may (if present in sufficient quantity) be a useful biological marker for foetal exposure to drugs (Klein *et al*, 1994)

smokers by using radioimmunoassay and gas chromatography over a decade ago (Manolis *et al*, 1983), procedures for drug testing using breath remain underdeveloped. The increasing sophistication of such technology is likely to improve both the availability and accuracy of such tests for wider clinical application.

Sweat

In recent years, remarkable advances in the sensitivity of analytical procedures have enabled the analysis of drugs on unconventional samples such as sweat. Sweat is collected by means of a 'sweat patch' applied to various sites of the skin (biceps, torso or back). All of the commonly used illicit substances, including buprenorphine and ecstasy, have been detected in sweat using precision chromatographic techniques (Kintz *et al*, 1996a; Skopp *et al*, 1996). Recently, sweat patches have been employed in drug treatment services to monitor patients prescribed methadone and have been reported to compare favourably with urine drug tests (Taylor *et al*, 1998; Kintz *et al*, 1998). Intrasubject variability and the influence of site application have been reported to be significant (Kintz *et al*, 1996b), and it is possible to adulterate the sweat patch by injection into or under the patch to cause a false positive (Fay *et al*, 1996) or false negative (Fogersom *et al*, 1997) test response.

However, little information is available on the characteristics of drug excretion in sweat under controlled dosing conditions, and sweat analysis is open to misinterpretation because of the difficulty of excluding topical contamination. Given the reported between-dose and between-subject variability, sweat patch test results cannot as yet be used to determine either the dose or the time of use (Burns & Baselt, 1995). Nevertheless, the sweat test does appear to offer an alternative non-invasive means of obtaining a cumulative estimate of drug exposure over a period of 7–21 days (Kintz, 1996). From a clinical viewpoint the sweat patch could serve as a useful monitoring device in surveillance of individuals on treatment and probation programmes. If applied to the skin with a tamper detection device, it could provide a more continuous monitor of drug exposure.

Body fluids and childbirth

The high increase in the number of pregnant substance users presenting at drug treatment agencies for treatment for their addiction, and at antenatal clinics, has led to a demand for improved

technology to assess the extent of drug ingestion by the foetus and/or neonate.

Breast milk

All drugs pass, to some extent, from plasma into human breast milk. The milk-to-plasma concentration ratio is the most commonly used index of drug distribution into milk, and is used to calculate the likely infant drug dose from a given maternal plasma concentration (Atkinson & Begg, 1990). The usefulness of human breast milk for assessing the extent of infant exposure to illicit substances has not been fully evaluated (Huestis & Cone, 1998). In Britain, drug-dependent nursing mothers are usually advised against breast-feeding. In many cases, this may be unnecessary as the total dose to which the baby is likely to be exposed is thought to be negligible (Atkinson & Begg, 1990). A particularly important case for consideration may be nursing mothers prescribed methadone. Breast-feeding has been advocated for methadone-maintained women (Batey *et al*, 1990), and may assist in reducing the severity of neonatal abstinence syndrome (Mack *et al*, 1991), although polydrug use is likely to complicate decisions made regarding suitability for breast-feeding.

Reports indicate accumulation of tetrahydrocannabinol (Astley & Little, 1990), amphetamine (Steiner *et al*, 1984) and cocaine (Dickson *et al*, 1994) in breast milk. Steiner *et al* (1984) argued 15 years ago that analysis of breast milk for drugs of misuse should be performed in cases of possible infant intoxication, but such tests have yet to become routinely available. Further research in this area is required since the extent to which the ingestion of illicit and psychotropic drugs by nursing infants may affect growth and development is unknown.

Meconium

Many substances have been detected in meconium including cannabis (Moore *et al*, 1996), methadone (Skolk *et al*, 1997), nicotine (Eliopoulos *et al*, 1996) and cocaine (Martin *et al*, 1996). However, analysis of drugs in meconium is currently only conducted by researchers.

Conclusion

Analysis of urine is currently the biological tool of choice for qualitative detection of illicit drug use. Quantitative accuracy usually demands the collection of a blood sample, although saliva may be an alternative in the future. The advantage of hair

sampling is its reflection of weeks rather than hours of recent use. Accurate interpretation of the screening tests within a clinical setting, alongside other relevant information, remains the key to the usefulness of any test.

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Multiple choice questions

- Regarding chain of custody:
 - chain of custody requires a witnessed urine sample
 - the patient can bring a sample previously voided to the clinic
 - temperature and specific gravity measurements should be taken to validate the specimen
 - written confirmation of the validity of the sample from the individual voiding the specimen should be sought
 - the patient can take the urine sample directly to the laboratory for immediate analysis.
- Regarding false positive and false negative tests:
 - a false negative is a negative finding in a sample from a patient known to have recently taken the drug of interest
 - a false positive test result is the incorrect determination of the presence of a drug of interest
 - there are commercially available preparations which can be used to produce false negative test results
 - the clinician is only interested in true positive drug tests
 - a drug taken legitimately may lead to a false positive test result in some circumstances.

3. Concerning sample collection:
- blood is easy to collect in large volumes
 - buccal cavity contamination is an important consideration when collecting saliva
 - the sweat patch is advantageous because it is difficult to adulterate
 - 24-hour urine sample collection is required for confirmation of drug test results
 - maintaining alignment, securing and identifying the cut ends of hair is important if segmentation is required.
4. About illicit drugs:
- commonly misused opiates including methadone all have the same metabolic end product
 - heroin is not excreted in urine
 - over-the-counter medication containing amphetamine-type drugs can be easily distinguished from illicit substances using immunoassay tests
 - cannabis is a short-acting drug
 - cocaine (parent drug) is detectable in urine for 6–8 hours.
5. About biological indicators:
- urine is best for quantitative measurements of drugs currently active in the body
 - hair provides a short-term alternative to urine
 - saliva is a potential alternative to blood sampling
 - urine provides a good qualitative indication of recent drug consumption
 - meconium is widely used to screen for evidence of illicit maternal drug use.

MCQ answers

1	2	3	4	5
a T	a T	a F	a F	a F
b F	b T	b T	b T	b F
c F	c T	c F	c F	c T
d T	d F	d F	d F	d T
e F	e T	e T	e T	e F

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