AUTOPSY, FINDINGS

Contents

Drug Deaths
Postmortem Drug Measurements, Interpretation of
Postmortem Drug Sampling and Redistribution
Organic Toxins
Fire
Drowning
Sudden Infant Death Syndrome

Drug Deaths

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Introduction

Deaths from natural or traumatic causes display specific anatomic features. The anatomic findings associated with drug abuse are rarely specific, nor are the toxicological findings that accompany them. Drug-takers are at increased risk for a variety of lifestyle diseases, including hepatitis, tuberculosis, and human immunodeficiency virus (HIV). If drugs are present at the time of death in an HIV-infected person, and they frequently are, then it is often difficult or impossible to determine whether HIV-related infection or drug abuse was actually the cause of death.

Even if no lifestyle diseases are evident, postmortem blood measurements are difficult to interpret and may be misleading. This situation comes about mainly because of issues related to drug tolerance. Very high blood drug concentrations do not necessarily prove that drugs were the cause of death, and the demonstration of very low drug concentrations does not rule out drug involvement, because anatomic changes favoring sudden death may persist long after drug use is discontinued. Before drawing any conclusion based upon postmortem drug measurements, the effects of a very long list of confounding variables must be considered. Given the nonspecific nature of the death certification process, investigators must supplement information derived at autopsy with the results of toxicological testing and scene investigation.

Accurate death certification begins with a thorough account of what was observed at the scene and an inquiry into the decedent's past medical history. Knowledge obtained from such an inquiry may, in fact, prove more useful than findings from the postmortem examination. Reliance upon only the autopsy, or only the toxicology testing, to the exclusion of the other sources of information, is almost certain to result in an inaccurate or completely mistaken diagnosis.

Scene Investigation

Overview

The type of drug most likely to be responsible for death varies by location. Even in the same city, certain drugs are more popular within some population subgroups than within others, a circumstance that may be of some diagnostic value. In San Francisco, methamphetamine is most popular within the gay community, but that is not the case elsewhere. While the death of a 40-year-old male methamphetamine user in San Francisco would not be very surprising; the death of a 22-year-old woman from methamphetamine poisoning, in Baltimore would rightly be viewed as suspicious.

A thorough investigation may reveal which drugs were taken and how they were administered. Were needles or smoking implements at the decedent's side? Are pill bottles in evidence? There is a good chance they will be absent, because the scene is likely to have been disturbed. It is almost the rule, rather than an exception, that friends of the decedent will have either stolen any remaining drugs or attempted to sanitize the scene so that it appears drugs were not involved in the death. Inspection of nearby trash bins may provide useful information. Even when friends or relatives make an effort to conceal the decedent's drug use, the attempts are unlikely to be sophisticated, and traces of drugs such as cocaine can, without too much difficulty, be detected on table and counter tops.

It is also important to obtain documentation about how the deceased had been behaving just prior to death. Was the individual a known drug-user, recently released from jail? Was the individual a binge drug-user? Any one of those factors could have decreased

the decedent's level of tolerance and converted a "recreational" dose of drug into a fatal one.

Drug-Specific Considerations

Needle-exchange programs are increasingly common, but most addicts are still forced to reuse syringes. It is likely that a syringe found at the side of a decedent will have been used many times previously. It follows that any drugs found in the syringe may, or may not indicate use by the decedent.

Much of the illicit drug supply is delivered by "body packers," transporting drugs concealed in their body cavities. Quantities in excess of one-half kilogram can be concealed in this fashion. Drugs are recovered when the courier arrives at his/her destination and takes a laxative. If one of the packets ruptures, death is the predictable result. Laxatives, passports, and foreign currency are likely to be found nearby, and readily suggest the cause of death. What at first sight might appear to be a case of ritual mutilation may, in fact, be a drug dealer's effort to reclaim drugs remaining in the body of a dead courier.

Psychotic drug-takers are an increasing problem. Some die alone, in their home or hotel room, their psychotic behavior evidenced by the destruction of their surroundings. Some may barricade their door against imaginary enemies. Taken in excess, stimulant-type drugs cause hyperthermia, both as a consequence of increased physical activity, and because of impaired heat dissipation. Accordingly decedents are often to be found in the shower, with cold water running, or surrounded by wet towels and ice cube trays.

If the drug user becomes psychotic in public, physical restraint will be needed, if not to protect the drug user, then to protect others. If death occurs during the struggle, the lethal outcome will be attributed to the process of restraint itself and to police misconduct. Unless the scene investigation is conducted appropriately, and the results made available to the pathologist prior to the autopsy, the actual cause of death may never be determined.

When death occurs during a police confrontation, a number of specific observations need to be recorded, but the most important function of the scene investigator is to notify the pathologist of the situation immediately. Most (though not all) psychotically agitated individuals who die suddenly are suffering from a syndrome known as excited delirium. This syndrome is associated with distinct, measurable neurochemical alterations that can be detected after death, but only if the brain is removed and frozen within 12 h. Standard protocols must be put in place to ensure that responsible authorities are notified as soon as possible. Having notified the responsible authority, other measures to be taken include the following.

1. The ambient air temperature and the temperature of the body at the scene must be measured. Not all patients with stimulant toxicity are hyperthermic, but many are, and if the temperature is never taken, the proof is never obtained.
2. The means of restraint and the position of the deceased must be documented, not only with photographs, but also with the testimony of as many witnesses as possible. This documentation is especially vital if application of a chokehold is alleged. If a chokehold is applied effectively, it will lead to loss of consciousness in 15–20 s. If a witness insists that the struggle lasted much longer than 15 s, then application of a chokehold becomes an unlikely cause of death.
3. The records of the paramedics and emergency field workers should be obtained, including records generated in the emergency ward. An electrocardiogram, even if only a one-lead rhythm strip, may help make the diagnosis of long QT syndrome or other heritable channelopathy. Recording of pulse occimetry data is now routine in many jurisdictions. If the percentage oxygen saturation during resuscitation and transport has been recorded, it may be possible to rule in or out death from "positional asphyxia."
4. Chemical incapacitating agents have little effect on the psychotically agitated, and their use is to be discouraged. However, if these agents have been used, the canisters must be collected and weighed, so the amount of spray discharged can at least be estimated. This is possible because the weight of all containers leaving the factor is very similar, and because officers must record each use of the spray. There is no assay for the measurement of pepper spray (the most widely used such agent in the USA) from biological matrices, but capsicum and other chemical incapacitating agents can easily be recovered from clothing and from skin, using methanol swabs. If the chemical agent cannot be recovered from facial skin, then it is reasonable to assume that the spray never entered the lung, and if it did not enter the lung, it cannot be the cause of pulmonary toxicity.
5. If resuscitation was attempted, investigators must thoroughly document what happened at the scene, and what efforts were made in the emergency room. It is especially important to know what measures were taken to establish an airway. Multiple attempts at laryngeal intubation can result in laryngeal bruising. If the history of intubation is

not recorded, bruising might be falsely attributed to manual strangulation.

Postmortem Examination

Deaths related to stimulant and opiate abuse tend to follow a stereotyped pattern. This pattern has been recognized for more than a century and consists mainly of pulmonary and cerebral congestion. Nonetheless, there are some key differences between opiate-related and stimulant-related deaths. The differences are mostly explained by the observation that stimulants tend to exert direct cellular toxicity while opiates do not. As a consequence, most of the anatomic changes observed in opiate abusers are secondary either to the materials injected along with their drugs, or to the occurrence of "lifestyle" diseases, such as HIV and hepatitis.

External examination of opiate abusers is much more likely to disclose sclerotic veins, or "track marks," because the diluents and excipients found in heroin are less water-soluble than those found in cocaine and methamphetamine and, therefore, are more toxic to veins. However, the practice of simultaneously injecting cocaine and heroin is now so common that nearly all intravenous drug users will have evidence of chronic injection injuries. Most of the materials used to "cut" heroin display a pattern of birefringence that can easily be seen under low power magnification. Crystals found in the kidney and liver tend to be smaller than those found in the lung, since the lungs themselves will have acted to sieve out the particles. Each of the different cutting agents has a characteristic pattern of birefringence that is unique and identifiable.

If petechiae or bruises are present, they should be photographed, if only because petechiae can form after death. If the absence of petechiae is not documented initially, false charges of incompetence or "cover-up" may result. A careful neck dissection is the only way to determine whether a chokehold or neck compression has been applied, but the thoracic organs and the brain must be removed before commencing the dissection. Removing the other organs first will prevent postmortem bleeding into the soft tissues of the neck. If this precaution is not taken, it may be falsely concluded that neck injury had occurred.

Hemorrhage around the larynx, and the presence of facial petechiae, can be evidence for strangulation, but they may also simply be an artifact, the result of unsuccessful attempts at establishing an airway. Bruising within the larynx, in the absence of bruising of the long muscles of the neck, is virtual proof that bruising was the result of attempted medical intervention, not assault.

Other external markers include "crack thumb," a callus seen on the medial aspect of the thumb, secondary to repeated use of butane lighters to heat crack cocaine (Figure 1). Burns on the lower lip, a consequence of smoking hot glass "crack pipes," are also common (Figure 2). Excoriations of the anterior chest wall are usually a sign of chronic opiate abuse. Heroin and other opiates (though not fentanyl and other synthetic drugs) cause mast cells to release histamine, and can result in intense pruritus.

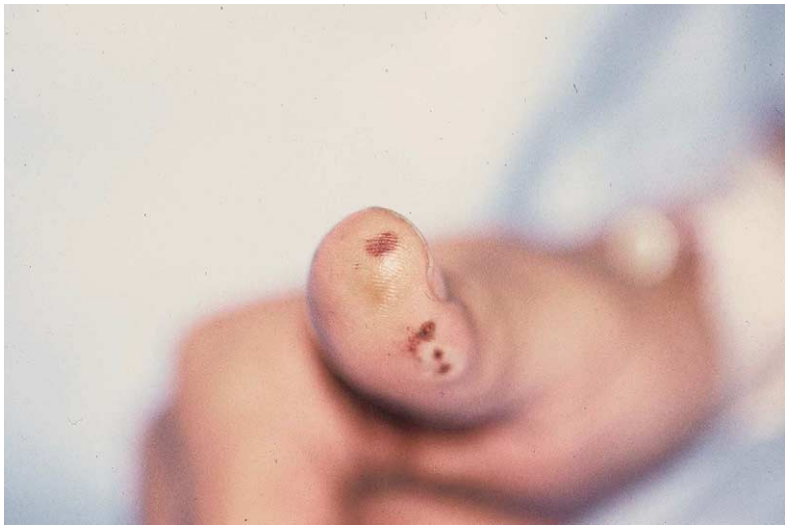

Figure 1 ''Crack thumb.'' Disposable butane lighters are often used to heat crack pipes. If used repeatedly, the lateral aspect of the thumb becomes calloused.

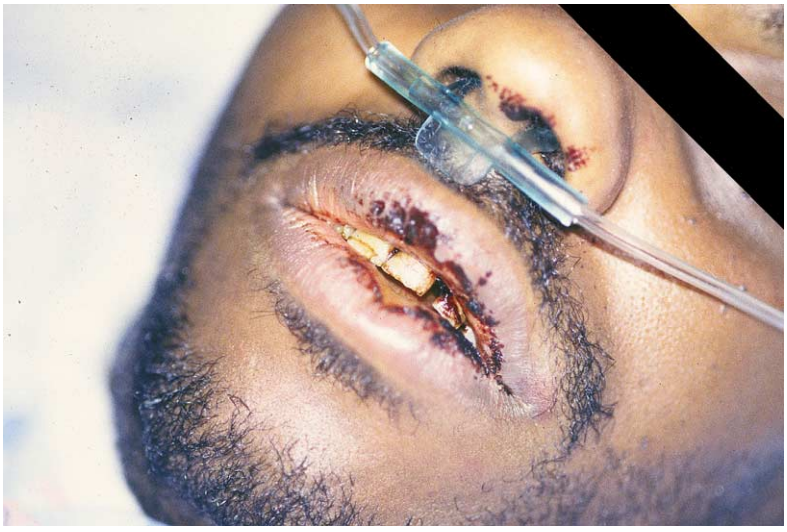

Figure 2 ''Crack lip.'' Frequent smokers of crack cocaine often burn their lips on the improvised pipes they use for smoking.

Crack lung is an increasingly common finding, with little to distinguish it from other types of pulmonary anthracosis. Emphysematous changes may be marked as well. Pulmonary edema is almost inevitably present, but the mechanism remains unknown. Edema fluid in cases of opiate overdose is usually high in protein content and tends to froth and foam like egg white. If the agonal period was prolonged, capillaries will have ruptured, leaving the fluid blood-tinged. Terminal aspiration is exceedingly common, and if the drug concentration of the stomach contents was high, then drug may redistribute through the lungs into heart blood, resulting in falsely elevated postmortem drug concentrations.

The heart must be carefully weighed and left ventricular wall thickness measured at several different locations. Multiple sections, particularly of the left ventricle and septum, should be retained for histologic examination. Increased heart size may only become apparent after the heart has been weighed, and the result compared to the weight predicted by standard nomograms. When such comparisons are made, the hearts of long-term stimulant abusers will be found to be at least 10% above predicted norms. Heart size is an independent risk factor for sudden cardiac death and the measurement may prove to be a very significant factor in determining the cause of death.

A number of other changes are commonly seen in chronic abusers, though they are not invariably present. Opiates impair gut motility, and obstipation is almost diagnostic for opiate abuse, although the frequency of this finding appears to be decreasing, perhaps because the opiates are being used along with other illicit drugs, like cocaine, that stimulate the gut. Infiltration of the portal triads, with lymphocytes and plasma cells, can be seen in either opiate or stimulant injectors. It seems increasingly clear that the infiltrates represent underlying infection with hepatitis C. Enlargement of the periportal lymph nodes is an unexplained but common finding in heroin users, but not in users of cocaine or methamphetamine. The nodes (especially in the gastroepiploic area) themselves will often be found to contain high drug concentrations.

Postmortem Toxicology

Postmortem redistribution is defined as the movement of drug down a concentration gradient after death. The redistribution process begins immediately and continues indefinitely, but the greatest changes occur within the first 24 h. Redistribution is much more likely to occur if a drug has a large volume of distribution, and also more likely if the drug is sequestered in either the lung (fentanyl), or liver (propoxyphene).

The process of postmortem redistribution accounts for the fact that postmortem blood testing is an extremely unreliable process. Blood concentrations measured in otherwise unspecified “heart blood” (or worse still, blood pooled in the thorax or abdomen) should be considered simply as a qualitative measurement, proving only that drug is present. Blood should be taken from the femoral vessels, but if they are not ligated first, aspiration of more than 20 ml of blood may yield blood from the liver or inferior vena cava, where concentrations of many drugs would be much higher than samples obtained elsewhere in the body.

Perimortem aspiration of stomach contents is very common, and can lead to very high drug concentrations within the bronchial tree. Simple diffusion out of the bronchi then allows drugs to traverse thin-walled pulmonary vessels. If aspiration occurs into the left lung, simple diffusion can result in high drug concentrations in cardiac blood. As a consequence of drug redistribution, blood samples obtained from different parts of the body are likely to contain different concentrations of the same drug. Methamphetamine concentrations in left heart blood are 1.9–2.6 times higher than blood samples taken from the right ventricle at the same time. Drug concentrations in the pulmonary artery blood may be 6–10 times as high as the concentrations in heart blood. Cocaine levels in the subclavian vessels fall after death, but concentrations in heart and femoral blood rise. Measurements of drug concentrations in left heart blood are especially likely to be misleading.

Measurement made in the bile is problematic. Some drugs concentrate in the bile, and if drug concentration is high in the bile, then postmortem liver concentrations will increase. However, if drugs have been used several days before death, they are unlikely to be detected in blood or urine, but may well still be present in bile.

A widely held misconception is that the site of administration can be determined by measuring drug concentration at that site. Drugs circulate throughout the body and appear in all body secretions. Cocaine recovered from vaginal swabs does not prove that the cocaine was applied vaginally, any more than cocaine recovered from nasal swabs proves it was applied nasally. In theory, the presence of extravasated drug might be used to identify an injection site, but only if drug was also measured in multiple skin samples from other parts of the body, and a substantial difference was demonstrated.

No valid scientific evidence exists to support the notion that the cause of death can be determined by consulting a reference table, or by comparing postmortem testing results with results from clinical therapeutic drug monitoring. Tolerance to both stimulants and opiates emerges rapidly, and even the presence of massive amounts of drug does not prove that a particular drug caused death, or even that the massive amount of drug detected at autopsy was nearly so massive during life.

If a drug's effects decrease as the dose is held constant, or escalating doses of drug are required to produce the same effect, tolerance is said to exist. Except in certain special, albeit very important circumstances, the degree of drug tolerance cannot be assessed after death. Multiple studies have shown that postmortem concentrations of drugs like cocaine, heroin, and methamphetamine are indistinguishable in those dying of drug toxicity, and those where the presence of drug is only an incidental finding (i.e., a heroin user who is murdered). Cross-tolerance to other opiates is limited, unpredictable, and cannot be assumed to exist. A chronic pain patient being treated with high doses of methadone, for example, might experience fatal respiratory depression after a much smaller dose of morphine.

Tolerance secondary to chronic stimulant abuse is associated with changes in dopamine receptor numbers and density, and the diagnosis of stimulant-associated excited delirium can be inferred from appropriate receptor measurements in appropriately preserved brain tissue. Lack of tolerance can be proven by the failure to demonstrate drugs in hair. The detection of drug in blood or other tissues, but not in the hair, proves that there has been no recent drug use. None of the exhumed Shipman murder victims in the UK had detectable morphine in their hair, though substantial amounts were detected in blood and liver tissue. The absence of morphine in the victims' hair proved that the decedents had no tolerance, and disproved suggestions in Shipman's medical records that some of the decedents were illicit drug takers.

The results of early studies suggested that postmortem morphine concentrations above 300 ng ml^{-1} were proof of toxicity. But values well in excess of 300 ng ml^{-1} may be seen as incidental findings in trauma victims who happen to be heroin abusers. One way to address this problem is by hair testing. Hair morphine levels can be used to identify which decedents were tolerant at the time of death and which were not. Morphine concentrations in the hair of active heroin users are much higher than those in abstinent users, and concentrations in overdose deaths are comparable to those seen in abstinent users. Although postmortem hair sampling is not yet a routine procedure, hair samples should be at least

Table 1 Some factors affecting postmortem drug measurement

- Age
- Bacterial metabolism
- Chiral variation
- Drug interactions
- Circulatory status
- Genetic polymorphism
- Glycolization
- Hepatic disease
- Hydration
- Kidney function
- Muscle wasting
- Protein binding
- Site dependence
- Tolerance
- Volume of distribution

collected and stored. Information derived from their analysis could be invaluable if questions about drug abuse should arise at some later date.

Conclusion

Pathologists responsible for determining the cause of death must integrate measurements and observations submitted by a small army of specialists. These specialists are likely to know far more about their individual fields than the certifying pathologist. However, none of these other specialists are physicians, and none are skilled in the process of differential diagnosis. While toxicologists and entomologists can reliably detect the presence of billionths of a gram of drug in blood samples or insect larvae, they are unlikely to know about the effects of hemorrhagic shock on plasma volume, or the proximity of the stomach to the liver. Attempts at directly relating postmortem blood drug concentrations to outcomes only seem reasonable to those unaware of just how many variables need to be considered (Table 1). It is the forensic physician's job to keep all these variables in mind.

See Also

Substance Misuse: Medical Effects; Cocaine and Other Stimulants; Herbal Medicine; Heroin; Substitution Drugs; Sedatives; Miscellaneous Drugs; Urine Analysis; Hair Analysis; Alternative Body Fluids Analysis; Patterns and Statistics; Crime

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Postmortem Drug Measurements, Interpretation of

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Introduction

Toxicological examination plays an important role in death investigation. The primary mission of the postmortem toxicology laboratory is to assist the medical examiner or coroner in determining the cause and manner of death. The most obvious use

for postmortem forensic toxicological analyses is in suspected drug intoxication and poisoning cases. Drug intoxications are not readily diagnosed at autopsy. In intravenous drug deaths, a recent injection site may be observable, and oral intoxications may be inferred from a large amount of unabsorbed tablet fragments in the stomach contents. However, other common anatomic findings such as pulmonary congestion and edema are nonspecific. Investigation of the scene where a death occurs may indicate the causative agent or agents. For instance, items such as medicine containers, syringes, or gas cylinders from the scene should be reported to the toxicology laboratory. Nevertheless, the function of the toxicology laboratory is to identify the substances present in the submitted postmortem specimens. Once these substances are identified and confirmed by an alternate analytical technique, they are quantified in appropriate specimens to determine whether these drug concentrations caused or contributed to death.

Toxicological investigations are important in deaths other than drug intoxications. For several reasons, many medical examiners' or coroners' offices routinely perform screening analysis for drugs on all homicides: many homicides are drug-related; the abuse of drugs may provide a motive for homicide; and an individual under the pharmacologic effects of drugs has a greater chance of committing or falling victim to homicides. Therefore, a drug-of-abuse screen provides answers to many of these questions.

In certain accidental deaths, impairment issues may have significant forensic relevance. Comprehensive testing for both therapeutic and abused drugs is routinely requested in driver motor vehicle fatalities to ascertain the potential role of drugs in the accident. Obviously, the well-documented role of alcohol in many motor vehicle accidents requires that alcohol testing be performed in these cases. However, drugs being taken therapeutically as prescribed may also be a factor in an accident.

Toxicological analyses may even be important in deaths due to natural causes. For instance, deaths from seizures occur with or without anatomic findings. The failure to identify anticonvulsant drugs in blood may indicate undermedication or noncompliance. Conversely, the presence of anticonvulsant drugs with no prior seizure history may require investigation. Patient compliance may also be an issue in deaths of individuals being treated for depression or mental illness.

This article will discuss the interpretive aspects of these analytical results. The techniques used to generate these analytical data will be discussed elsewhere. This article will include a number of subsections. There will be a discussion of specimens and the interpretive value of each. This will be followed by a discussion of how the analytical process impacts the interpretation of results. This is followed by a discussion of interpretive issues and complications associated with the finding of ethanol and/or postmortem cases.

Specimens Used for Analytical Toxicology

Blood

The single most important specimen to be collected is blood. Unlike clinical specimens where serum or plasma is tested for drugs, postmortem blood specimen analysis is performed on whole blood. As a result, the interpretation of postmortem blood concentrations using clinical serum or plasma data is fraught with difficulties. Blood should be obtained during all inspections and limited or complete autopsies. Ideally, two blood specimens should be collected, one from the heart and the other from a peripheral site, such as the femoral or subclavian veins. Quantification of drugs in blood is better correlated with toxicity or fatality. Blood quantifications must be interpreted in light of available history. A high concentration of a drug or a group of drugs in the blood of an individual with suicidal intent, a suicide note, and no anatomic cause of death at autopsy would be consistent with a suicidal drug or multiple drug intoxication. A large ratio of parent-to-metabolite concentrations may indicate an acute death. A therapeutic concentration in postmortem blood in an individual treated in the hospital for several days may indicate much higher concentrations at an earlier time. Often, hospital laboratories perform drug testing on urine specimens without associated blood quantifications. Therefore, the postmortem laboratory should obtain hospital blood specimens so that toxicity can be assessed. Of course, the clinical picture as documented by the hospital is extremely critical to this overall assessment.

In certain situations, heart blood can be contaminated either by trauma or from the release of drugs from tissue sites; in these cases, the alternate blood specimen can be used for interpretation of results. Blood from subdural or epidural clots should also be collected. These specimens could be useful when there is a period of time between an event and death.

Bile and Urine

Two useful postmortem specimens that should be collected in every case, if available, are bile and urine. The utility of urine in postmortem cases is similar to its uses in other types of drug testing.

Many drugs and metabolites are present in higher concentration in urine than in blood. Drugs also remain in the urine for days or longer after use. Moreover, bile can concentrate certain drugs such as opioids and benzodiazepines. However, the presence of drugs or metabolites in bile or urine will indicate exposure, but assessment of toxicity or impairment is usually impossible. The best that can usually be concluded is that the drug or drugs were used some time in the recent past, hours to days, depending on the drugs' pharmacokinetics profile.

Liver

In the absence of blood, liver is a useful alternative specimen for drug quantification. Drug metabolism occurs in the liver, so parent drugs and their metabolites may be present in higher concentrations in the liver than in the blood, thus making detection easier. Furthermore, many drugs, such as the tricyclic antidepressants, are sequestered in the liver.

Stomach Contents

In overdose drug ingestions, stomach contents can provide easy identification of the substance or substances taken if intact tablets are present. A large amount of drug would also be present in the stomach contents, thus facilitating analytical identification. Estimating the amount of drug in stomach contents may also give information about the intent of the decedent. For instance, if the amount of drug present in the stomach contents is inconsistent with the amount that should be present following proper therapeutic use, it may be suggestive of an intentional overmedication. There is one important caution in interpreting stomach contents quantifications: the presence of a large amount of drug or drugs in the stomach contents does not mean that drug intoxication has occurred. This must be combined with the quantification of the drug or drugs in the blood or liver, since stomach contents are unabsorbed material and substances must be absorbed before toxicity can occur.

Analytical Procedures

Although this article will not be discussing the analytical process, there are aspects of the analytical process that must be considered in the interpretation of ethanol and drug results. For instance, it is impossible for a toxicology laboratory to test for all available drugs when performing comprehensive drug testing. Instead, a laboratory's routine testing procedures are established to identify a large number of therapeutic and abused drugs or drug classes. Not every drug available can be detected in a routine testing protocol; even within a drug class, some drugs may be identified and others may not. A result of "no benzodiazepines detected" may indicate that an immunoassay was performed and the response was less than the cutoff calibrator. However, many benzodiazepines differ in their response in the immunoassay. Each laboratory must determine the type of testing offered based on available resources; however, it is crucial for the laboratory director to understand the capabilities of the routine testing procedures used by the laboratory. These facts reinforce the need for a drug history when a case is submitted. If the suspected agent is not identified routinely, then the medical examiner or coroner must decide as to the importance of this drug measurement in the ultimate certification of death. When the information is important, the toxicology laboratory may perform special testing in-house or send the specimen to a reference laboratory for testing.

It is also important that the laboratory be aware of the sensitivity or detection limits for the drugs included in the routine comprehensive testing procedures. Some drugs may only be detected in toxic or overdose amounts. This would be sufficient if the question concerns drug intoxication. However, if the issue involves drug compliance or impairment from therapeutic use of the drug, then the routine testing procedures may be inadequate. In those cases, additional testing would be required.

Ethanol

When ethanol is consumed before death, the interpretation of blood ethanol concentrations in postmortem specimens is similar to the interpretation of blood specimens in living individuals. According to multiple scientific studies, a blood ethanol concentration of $0.08\,\mathrm{g\,dl^{-1}}$ indicates that all individuals would show some impairment due to ethanol. This impairment would manifest itself in reductions in judgment, attention, and abilities in multitasking events. As the blood ethanol concentration increases, more overt symptoms of alcohol impairment would be observable. There are individual differences to these effects. In general, at a given blood ethanol concentration, less impairment will be demonstrated in a chronic drinker than would be displayed by the occasional or social drinker. A blood ethanol concentration at or above $0.40\,\mathrm{g\,dl^{-1}}$ can be consistent with causing death due to ethanol intoxication in the absence of other pathological findings. There are a number of published tables that correlate ranges of blood ethanol concentrations with effects.

In cases where there is a period of time between an injury and death, analysis of the more common

postmortem blood specimens may not reflect the blood ethanol concentration at the time of injury, since ethanol metabolism will continue during the period of survival. In those cases, analysis of other specimens such as hospital admission blood or other samples collected closer to the time of injury would be more relevant in determining the role of ethanol in an injury. If no antemortem specimens were collected, blood from sequestered hematomas, such as subdural, epidural, or intracerebral blood, may better approximate the blood ethanol concentration at the time of injury. The theory behind this practice is that ethanol is not metabolized to the same extent as would occur in circulating blood. Nevertheless, the development of these hematomas is not instantaneous; as a result, the blood ethanol concentration will not be homogeneous. Moreover, the water content of the clot may differ from the water content of the circulating blood, further complicating the interpretation of the measured ethanol concentration.

The interpretation of postmortem ethanol concentrations is complicated by the potential artifactual increase in ethanol concentrations after death. For example, in trauma cases, blood from the heart, a common site of postmortem blood collection, may be contaminated by stomach contents. If there is any residual ethanol remaining in the stomach contents, this will cause an artificial increase in the heart blood ethanol concentration when the stomach contents come in contact with the heart. In these cases, blood from a peripheral site (e.g., femoral vein), away from the site of trauma, should be collected and analyzed for ethanol.

Although most embalming fluids contain methanol and do not contain ethanol, these fluids may also be a source of ethanol contamination if the specimens are not collected prior to embalming. If the issue of ethanol consumption arises after a body is embalmed, it is recommended that some of the embalming fluid be obtained and analyzed for the presence of ethanol to determine its contribution to the postmortem blood concentration.

Bacteria, yeast, and molds can, under proper conditions, produce ethanol. A number of substrates can be converted into ethanol by these microorganisms. Glucose is the primary substrate that may be converted into ethanol; therefore, any tissue with high concentrations of glucose or glycogen is susceptible to postmortem ethanol production. Blood, liver, and muscle are examples of specimens with high sugar concentrations in which significant concentrations of ethanol attributed to postmortem formation have been measured. Conversely, urine and vitreous humor are ordinarily free of the combination of glucose and microorganisms necessary to produce ethanol. Other substrates for ethanol production include lactate, ribose, and amino acids. The mechanism of ethanol production from sugar is glycolysis, which is the first step in the normal breakdown of glucose.

There are a number of factors that can or should be considered when determining whether measured ethanol occurred due to antemortem consumption of alcohol or microorganism activity. For example, witnessed drinking by the decedent prior to death is obviously significant. While there is often an underestimation of the amount of ethanol consumed, the observation that the individual was drinking is usually reliable. Unfortunately, drinking history immediately prior to death is often unavailable, especially in the case of unattended deaths.

Although conditions for a body to putrefy or decompose may vary tremendously, there are a number of common characteristics of a decomposed body. The most striking trait is the foul odor associated with the body. Bloating, discoloration, skin slippage, and insect infestation are also common features associated with decomposition. Insect infestation, such as with maggots, is frequently present in decomposed bodies and is often helpful in ascertaining the length of time that an individual has been dead. When signs of putrefaction are present, postmortem production of ethanol must be considered as possible if not probable. Unfortunately, the amount of ethanol produced is highly variable between decedents; two bodies kept in the same conditions for the same length of time can produce widely different amounts of ethanol. This issue is further complicated if the individual had actually been drinking prior to death. In that scenario, the postmortem alcohol measured might be due to both antemortem consumption and postmortem formation.

When the body absorbs ethanol, it distributes according to the water content of each tissue or fluid. For example, since a given volume of vitreous humor and cerebrospinal fluid contains more water than an equal volume of whole blood, their ethanol concentrations will typically be higher than the blood ethanol concentration after equilibrium has been reached. Conversely, liver and brain will typically have lower ethanol concentrations than the blood ethanol concentration after equilibrium is achieved.

The distribution of ethanol between these specimens can provide a strong indication as to whether the measured ethanol resulted from drinking or decomposition. For example, one approach to multiple specimen analysis is to analyze blood, vitreous humor, and urine. In the postabsorptive phase of alcohol metabolism, the vitreous humor to blood ethanol concentration ratio is about 1.2 and the

urine to blood ethanol concentration ratio is about 1.3, although there are wide variations in these ratios. The liver to blood ethanol concentration ratio is approximately 0.6; the average brain to blood ethanol concentration ratio is approximately 0.7–0.9. If the measured postmortem ethanol concentrations yield similar ratios to those established for these specimens, then it is reasonable to conclude that the measured ethanol resulted from drinking. Moreover, vitreous humor and urine are two specimens that are relatively resistant to the putrefactive process and thus are not sites generally associated with postmortem ethanol formation. If the blood ethanol concentration is positive and the vitreous humor and urine ethanol concentrations are negative, this is a strong indication that the ethanol concentration in the blood is the result of decomposition.

Microorganisms that produce ethanol may also be capable of producing other volatile substances. One of these volatile substances is acetaldehyde. However, since acetaldehyde is also a metabolite of ethanol, its identification in biological specimens cannot be used as a marker for decomposition ethanol production. Another volatile commonly seen as a putrefactive product is *n*-propanol. *n*-Propanol and *n*-butanol are not identified in individuals drinking alcoholic beverages and, therefore, are good markers for decomposition ethanol formation. *In vitro* studies have identified other volatile substances that may be produced during the decomposition process. Volatiles that have been identified include acetone, isopropanol, *t*-butanol, isoamylalcohol, and *n*-amylalcohol. In a manner similar to ethanol formation, the specific volatile or volatiles produced is dependent on putrefactive conditions.

In addition to identifying unique products of postmortem formation, one can also assay for products unique to ethanol consumption. Ethylglucuronide, a phase II metabolite of ethanol, would not be produced by microorganisms and would indicate ethanol production before death.

A number of studies have been performed that describe the production of ethanol in postmortem blood. These studies can be summarized by the following conclusions:

1. When ethanol is produced postmortem, the ethanol concentration is usually less than $0.07\,g\,dl^{-1}$.
2. Production of ethanol concentrations greater than $0.10\,g\,dl^{-1}$ has been reported.
3. The production of ethanol due to decomposition is variable and is dependent on the species of microorganism present, the available substrate, time lapse since death, and the temperature and other environmental conditions.

Although urine has been shown to be generally immune to the effects of postmortem production of ethanol, several studies have indicated that the combination of glucose in the urine, a condition that often occurs in diabetics, and a *Candida albicans* infection can result in the production of large amounts of ethanol. Both components are required for ethanol production to occur and it will not occur in the absence of either the glucose or the microorganism. This can be demonstrated in the laboratory by performing serial analyses of the urine for ethanol over several days and observing the increase in ethanol concentration over time.

Drugs

In many respects, the interpretation of postmortem ethanol concentrations is much simpler than the interpretation of postmortem drug concentrations. First, the pharmacokinetics of ethanol is less complicated than the pharmacokinetics of drugs. The route of ethanol administration is almost always oral. Ethanol distributes according to the water content of the fluid or tissue; as such, distribution ratios between fluids and tissues have been well established. These ratios can then be used to determine the individual's absorption status (absorptive or postabsorptive). At ethanol concentrations associated with drinking, elimination is zero-order, that is, the blood ethanol concentration decreases by a constant amount per hour; this allows an estimation to be made of an ethanol concentration at an earlier time. By contrast, drugs can be administered by a variety of routes, including oral, smoking, snorting, intravenous, or intramuscular. The pharmacokinetics of a particular drug may be different depending on the route of administration. For instance, delta-9-tetrahydrocannabinol (THC), the active component of marijuana, is metabolized differently depending on whether the marijuana is smoked or ingested orally. Oral ingestion of THC produces higher concentrations of the hydroxy metabolite in the plasma than does the smoking route.

Drugs distribute to different extents throughout the body. Due to extensive plasma protein binding, some drugs remain mostly in the vasculature; other drugs are sequestered in specific tissues or distribute throughout the body. Most drugs are eliminated by first-order kinetics, with elimination half-lives varying between hours and days among drugs. Even a particular drug may show significant variation between individuals, depending on the individual's age, gender, health status, or genetics. Some drugs are converted to active metabolites that must be incorporated into the overall interpretation.

Given these pharmacokinetic differences between drugs and between individuals, the prediction of a dose based on postmortem measurements is not reliable. Even the measurement of total body burden, that is, measuring the concentration of a drug in a tissue and multiplying by the tissue weight, has limited utility in predicting dose. One would need to measure the parent drug and all metabolites to reach a useful number. If a drug accumulates or is taken chronically, the measured amounts may reflect prior usage. Moreover, even within a tissue group, such as muscle, there are differences in concentration as a function of tissue site.

Correlating effects with postmortem measurements is also more complex with drugs. The effects of ethanol are generally correlated with the blood ethanol concentration. For a number of drugs, a therapeutic range has been determined. These ranges have been collected from therapeutic drug-monitoring data and represent plasma concentrations where optimum therapeutic benefit combined with minimal toxicity is achieved. It cannot be overemphasized that postmortem blood is highly variable in terms of homogeneity and hematocrit and that the use of clinical serum data alone to interpret postmortem blood concentrations should be done with caution. Antiepileptic drugs, some cardioactive drugs, and some antidepressant drugs would be examples of drugs where therapeutic ranges have been established in living individuals. Unfortunately, only a small number of therapeutic drugs have therapeutic ranges associated with them. Furthermore, none of the illicit drugs encountered by the postmortem forensic toxicologist have normal ranges established.

In an attempt to provide assistance in the interpretation of postmortem drug concentrations, a number of tables have been compiled. These tables may list therapeutic, toxic, and lethal concentration ranges for a large group of therapeutic or abused drugs. These compilations may be based on antemortem pharmacokinetics studies, literature references of poisonings that were successfully treated, or case reports of fatalities. It must be strongly emphasized that these tables are at best a guide or a starting point when interpreting postmortem drug concentrations. First and foremost, postmortem blood is often quite different than blood collected from living individuals. The pH of postmortem blood is generally acidic. The hematocrit of postmortem blood can vary widely, depending on body position and collection techniques. Postmortem blood is not homogeneous. When a drug is first absorbed, the blood closest to the site of absorption will have the highest drug concentration while blood remote to this site will have the lowest drug concentration. As the drug distributes, differences in concentration between blood sites is reduced. There are also postmortem factors that contribute to heterogeneity. Therefore, the use of these tables may lead to erroneous conclusions when used to interpret postmortem blood results.

Postmortem Redistribution

One of the early assumptions in the interpretation of postmortem drug analysis was that, at death, drug pharmacokinetics stopped. That is, drug absorption, distribution, and metabolism ceased once the individual died. Therefore, specimens could be collected some time after death and the analytical data generated reflected the situation at death. Unfortunately, over the past 25 years, it has become well established that this assumption is not valid in a large number of circumstances. In general, blood concentrations of many basic drugs such as tricyclic antidepressants and antimalarial drugs are site-dependent. The heart blood drug concentration will usually exceed the drug concentration in blood from peripheral sites such as the subclavian, iliac, or femoral veins. One explanation for this observation is that, after death, drugs bound to tissues during life will be released into the surrounding blood. For instance, digoxin, a cardiac glycoside used to treat congestive heart failure, accumulates in the heart. After death, the drug releases into the heart blood, causing an increased drug concentration in the postmortem heart blood. Subsequent analysis of this sample will result in an elevated digoxin concentration. If this concentration were interpreted in terms of clinical therapeutic drug-monitoring data, the concentration would suggest that toxicity due to digoxin was involved in the case. Studies indicate that vitreous humor digoxin analysis provides more meaningful interpretive information in these cases.

Drugs may be released from other tissues as well. Tricyclic antidepressants were among the first group of drugs where this postmortem redistribution phenomenon was documented. During life, tricyclic antidepressants are sequestered in the liver; after death, the drugs are released from the liver into the nearby blood. Studies have also indicated that these drugs release from the lung during the postmortem interval. Subsequent movement into the heart blood can lead to elevated drug concentrations when this specimen is measured. It is recommended that, in addition to quantifying the drug in a peripheral blood specimen, the liver should also be quantitated. Liver tricyclic antidepressant concentrations are 10–50 times higher than are blood concentrations. Since these concentrations are so high, loss of the drug during the postmortem interval would not be as significant in terms

of reflecting the liver concentration at death. By comparing the liver and blood concentration ratios, one can better interpret the analytical findings.

Besides the distribution of absorbed drug, a number of studies have documented that, after death, unabsorbed drug from the stomach contents can distribute into fluids and tissues. This has been demonstrated with barbiturates and tricyclic antidepressants.

There are a number of other general observations with regard to the postmortem redistribution phenomenon. Drugs with high volumes of distribution and which are sequestered in tissues (e.g., tricyclic antidepressants or phenothiazines) exhibit the potential for postmortem redistribution. Redistribution follows the concentration gradient, that is, movement from an area of high concentration to an area of low concentration. Not all drugs display this phenomenon. Finally, the interpretation of postmortem blood concentrations must be made in the context of the specimen location.

Postmortem Decreases in Drug Concentrations

In addition to spuriously elevated drug concentrations in blood that result from postmortem redistribution, some drugs continue to be broken down after death. That means that the drug concentration measured at the time of sample collection may be significantly lower than the drug concentration that would have been measured immediately at death. Drugs that break down after death are associated with certain functional groups. Drugs that have a nitro group, such as clonazepam and flunitrazepam, will be reduced to their amino analogs after death. *N*-oxides such as chlordiazepoxide are also unstable postmortem. Sulfur-containing compounds may also display postmortem instability. Hydrolytic enzymes retain activity after death; therefore, ester compounds may be susceptible to their activity. The ester most commonly encountered in postmortem forensic toxicology that displays this characteristic is cocaine. Cocaine contains two ester moieties. After death cocaine is hydrolyzed almost exclusively at the phenyl ester by plasma pseudocholinesterase to yield ecgonine methylester. The rate of hydrolysis has been shown to be dependent on blood pH and temperature, with higher temperatures and pH increasing the rate of hydrolysis. The loss of cocaine in unpreserved blood can be dramatic. Acidifying blood to pH 5 inhibits chemical hydrolysis and 2.0% sodium fluoride inhibits enzymatic hydrolysis. These conditions resulted in no cocaine loss over 200 days at refrigerated (4 °C) and frozen (–15 °C) temperatures and for at least 60 days at room temperature.

Postmortem bacterial activity may also cause a decrease in drug concentration. For example, bacterial enzymes can hydrolyze the glucuronides of morphine, leading to decreased concentrations of the glucuronides and increased concentration of free morphine.

Even if the measured blood concentration of a drug or drugs reflects the concentrations at death, interpretation of concentrations by itself is problematic. Often, there is an overlap between therapeutic and toxic concentrations of drugs. One reason for this overlap is tolerance. Tolerance is defined as the effect that results from the chronic use of a drug where a larger dose becomes necessary to achieve the original desired effect. Tolerance is usually acquired and develops more rapidly to some drug effects than to other effects. Tolerance may result from a number of mechanisms. Pharmacokinetic tolerance refers to the change in drug disposition with continued drug use. This may refer to a reduction of drug reaching a target organ or an alteration in metabolism. Learned tolerance refers to a reduction in drug effects due to learned compensatory mechanisms. Cross-tolerance may also occur within a drug class and between drug classes with similar pharmacological effects. There is cross-tolerance between central nervous system (CNS) depressants such as barbiturates and benzodiazepines.

The prototypical example of tolerance affecting the interpretation of drug concentrations is with opioids such as morphine, methadone, oxycodone, and fentanyl. A blood concentration that would produce toxicity in an opioid-naive individual may not produce toxicity in an opioid-dependent individual. Blood opioid concentrations in patients receiving them for pain often overlap the concentrations found in addicts. There is also an overlap in blood opioid concentrations between dependent individuals who die of opioid intoxication and those who die from other causes. The proper interpretation of postmortem blood opioid concentrations requires knowledge of a number of factors:

1. Were there any other findings that could account for death?
2. Were opioids prescribed for medical reasons?
3. Was the decedent an opioid abuser?
4. Was the abuser being treated for this addiction?

It is only with this additional information that a meaningful interpretation of the analytical findings can be made.

Drug Interactions

A significant factor complicating the interpretation of postmortem ethanol and drug concentrations is the presence of multiple drugs in the same case. The effects of a particular drug may be affected by the concomitant use of ethanol or other drugs. These

interactions can be additive, synergistic, potentiating, or antagonistic. An additive effect indicates that the total effect of a drug combination is the sum of the effects of the individual drugs. A synergistic effect means that the total effect of the drug combination is greater than the sum of the effects of the individual drugs. Potentiation is defined as an increase in the effect of a toxic substance acting simultaneously with a nontoxic substance. Antagonism refers to the canceling of effects of one drug by the simultaneous administration of another drug.

A number of interactions between ethanol and drugs have been characterized. For example, a synergistic effect in CNS depression is seen when ethanol and barbiturates are co-administered. Studies evaluating the behavioral effects of the combination of benzodiazepines and ethanol indicate an additive depressant effect on most measures of performance. In general, the behavioral effects of the benzodiazepines are very similar to those of ethanol and the two drugs in combination exacerbate the overt effects and apparent intoxication of each drug alone. When ethanol and opioids are co-administered the CNS depression and behavioral impairment are, at minimum, additive. This means that even if a group of these drugs is present in apparently therapeutic amounts, the combination of these drugs with or without ethanol may be sufficient to account for death.

The pharmacokinetics of a particular drug may also be affected by simultaneous use of ethanol and/or other drugs. The cytochrome P450 (CYP) system is a group of enzymes that are involved in the phase I metabolism of most drugs. Drugs that are metabolized by the same isozyme will compete for binding sites on the isozyme, leading to decreased metabolism for the drug with lower enzyme affinity. Although there are 12 CYP gene families, there are a smaller number of isozymes that are responsible for most drug metabolism. Therefore, it is quite possible that two co-administered drugs may be metabolized by the same isozyme. The drug that has a reduced metabolism will be detected in higher concentrations in the blood, possibly leading to toxicity. Therefore, an elevated postmortem concentration may be due to a decrease in metabolism as opposed to an overmedication. This has great significance in assigning a "manner of death."

Drugs that induce or inhibit drug metabolism may be another example of a pharmacokinetic drug interaction. The barbiturates have been known for a long time to be a CYP inducer. Enzyme induction leads to a decreased blood concentration of the drug affected by this induction. Conversely, enzyme inhibition leads to an increased concentration of the affected drug. Cimetidine and ketoconazole inhibit oxidative drug metabolism by forming a tight complex of the ferrous ion of CYP.

There are also genetic differences in drug metabolism. For example, individuals may be fast or slow metabolizers of a particular drug. Acetylation of procainamide to *N*-acetylprocainamide and demethylation of dextromethorphan show biphasic distribution of metabolic rates. Thus, the interpretation of parent to metabolite ratios must be interpreted in the context of these differences.

The combined use of ethanol and cocaine results in the formation of a unique metabolite, cocaethylene, by means of a transesterification process that occurs in the liver. The half-life of cocaethylene is slightly longer than cocaine, it is more toxic than cocaine, but it exhibits the same type and degree of CNS stimulation as cocaine. Therefore, the overall toxicity due to cocaine is increased when it is used in combination with ethanol.

Histologic Evidence of Drug Toxicity

As mentioned earlier, most deaths due to drugs are not associated with specific anatomic findings that enable the pathologist to assign the drugs as the cause of death. There are examples of drugs causing death as a result of specific damage to tissues that may be observed histologically. Methylenedioxymethamphetamine (MDMA, ecstasy) causes rhabdomyolysis and renal tubular breakdown. Another example of a drug causing tissue damage is acetaminophen (paracetamol). Acetaminophen intoxication demonstrates a multistage profile. The initial stage that occurs up to 1 h after ingestion produces nonspecific symptoms such as nausea, vomiting, and anorexia. This is followed by a period of apparent improvement; however, abnormal liver function tests do occur. Within 3–5 days of ingestion, hepatic necrosis occurs due to the formation of a toxic metabolite that binds to hepatic DNA. If untreated, death results from this liver necrosis. Postmortem blood analysis would most likely be negative for acetaminophen. Nonetheless, the death is due to liver necrosis caused by acetaminophen toxicity. This "drug death" would be identified by the pathologist during gross and microscopic examination of the body and not by the toxicologist performing a drug analysis.

Histologic evidence of toxicity can also be observed after the chronic abuse of drugs. Fatty liver, cirrhosis, cardiomyopathy, and pancreatitis are common findings in chronic abusers of ethanol. There are also cardiovascular changes such as scarring that may be observed in chronic cocaine abusers.

Conclusion

Postmortem ethanol and drug results, like clinical laboratory results, cannot be interpreted in isolation. Rather, they must be interpreted in the context of the particular case. If the analytical methods used do not identify a particular analyte of interest, then a final report of "no drugs detected" may be misleading. The interpretation of a blood ethanol concentration is dependent on the absence or presence of putrefaction. A particular blood morphine concentration will have different meanings based on the presence or absence of acute trauma and on the prior use history of the decedent. Certain drug concentrations may be artificially increased during the postmortem interval. Conversely, an unstable drug may be reduced in concentration during the postmortem interval. Finally, drugs may work together to produce toxicity that would not occur if the drugs were not taken in combination.

See Also

Autopsy, Findings: Postmortem Drug Sampling and Redistribution; **Drug-Induced Injury, Accidental and Iatrogenic**; **Pharmacology of Legal and Illicit Drugs**; **Substance Misuse:** Cocaine and Other Stimulants; Heroin; Sedatives; Miscellaneous Drugs; Alternative Body Fluids Analysis

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Postmortem Drug Sampling and Redistribution

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Introduction

The sample most commonly used for postmortem toxicology is blood, and the analysis most commonly performed is for ethanol. Tissue samples other than blood may be used for alcohol analysis when blood is not available, because of the condition of the body, or to provide corroborative or additional data for interpretation. For the analysis of therapeutic drugs and drugs of abuse, blood is invariably the sample of choice, but for some poisons other tissues such as liver, kidney, or hair may be the optimum samples. In general the purpose of a postmortem analysis for drugs is to determine as accurately as possible the concentration of the drugs that existed in blood at the time of death, in order to assess the likelihood of drug toxicity, and in particular whether the death can be explained by the drug concentration found. Invariably, the blood sample obtained for analysis at autopsy is taken many hours or days after death. During this interval between death and blood sampling, drug concentrations in blood, and other biological fluids and tissues, may change significantly. This is true for most, if not all, drugs. The causes of these postmortem drug changes are complex. An increasing

awareness of their importance over the past few decades has resulted in significant changes in the way in which blood samples are obtained at autopsy and how the drug concentrations in those blood samples are interpreted. An understanding of postmortem drug changes underpins both the rationale for the method of postmortem blood sampling for analysis as well as the rationale for the interpretation of the analytic results. Drug and metabolite concentrations in postmortem blood are interpreted by comparison with previously reported concentrations corresponding to therapeutic, toxic, and fatal conditions. Pharmacokinetic data obtained from drug studies in living volunteers cannot be applied directly to analytical results obtained from a postmortem blood sample.

Postmortem Drug Redistribution

Although clinical pharmacokinetics cannot be applied directly to postmortem toxicology, it provides a good starting point for an understanding of the most significant of the postmortem drug changes, namely postmortem drug redistribution. Volume of distribution (V_d) is an important clinical pharmacokinetic concept. The V_d is a theoretical volume that does not correspond to any physiological space. It is the hypothetical volume of body fluid that would be necessary if the total amount of drug in the body were distributed at the same concentration as in plasma. The V_d is expressed as liters per kilogram of body weight. For a drug that distributes to plasma only, the V_d approximates 40 ml kg^{-1}. A V_d of 160 ml kg^{-1} implies a drug with extracellular distribution only. For a drug that has total body water distribution and can enter cells, for example, ethanol, the V_d approximates 640 ml kg^{-1}. Some drugs have an apparent V_d greater than that of total body water and for these drugs, tissue depots sequester the high drug concentration. The V_d of several commonly encountered drugs are set out in Table 1. If a drug has a high V_d then this indicates that, in life, it concentrates in tissue depots, such as the liver and the lungs. Following somatic death, the death of the cells of these tissue depots of drug permits passive diffusion of the drug along concentration gradients within the body. Since at death the concentration of drugs with a high V_d is lower in blood than in solid organs such as lung and liver, drug diffuses from the solid organs into blood to raise the blood drug concentration significantly.

Postmortem drug redistribution is the postmortem elevation of drug concentrations in blood as a result of diffusion from drug depots in solid organs. To permit this postmortem diffusion process, factors must come into play that allow for the release of the drugs from their binding sites in the solid organs.

Table 1 Volume of distribution (V_d) of commonly encountered drugs

Drug	V_d *(l kg^{-1})*
Acetaminophen (paracetamol)	0.75–1
Amphetamine	3–5
Amitriptyline	18–22
Aspirin	0.15
Caffeine	1
Cocaine	1.2–1.9
Diazepam	0.95–2.0
Digoxin	5–7
Imipramine	11–16
Lysergic acid diethylamide (LSD)	0.27
Methadone	5
Morphine	3.2 (i.v.)
Phenylcyclidine (PCP)	5.6–6.8
Trazadone	0.89–1.5
Triazolam	0.8–1.3
Trimipramine	20–50

These are likely to be complex physicochemical changes occurring as part of the processes of autolysis and, later, putrefaction. Changes in pH, the tissue-binding characteristics of the drug, and cell membrane integrity are all probable elements. Cell death itself brings to an end any energy-dependent drug-concentrating systems. The loss of cell membrane integrity is paralleled by the release of intracellular enzymes from the solid organs into the blood. It is this phenomenon that results in the artifactual postmortem elevation of cardiac myocyte and hepatocellular enzymes. If such large molecules as these enzymes pass rapidly into the blood postmortem, then it is hardly surprising that much smaller drug molecules do so. Postmortem drug redistribution into blood is well established within hours of death and is typically marked by the time of autopsy which is commonly a day or even 2–3 days after death.

Drugs are weak acids or bases and in solution they become ionized when they lose or gain a hydrogen ion. The degree of ionization of a compound depends on both its specific pK_a and on the pH of the solution in which it is dissolved, a relationship described by the Henderson–Hasselbalch equation. Since the lipid-soluble form (nonionized) of a weak electrolyte is the species that crosses cell membranes, organic acids are more likely to diffuse across membranes when they are in an acid environment whereas a basic environment favors diffusion of bases across membranes. In this way drugs become trapped in the compartment in which they are more ionized because ionized (polar) compounds do not easily cross cell membranes. In life, intracellular fluid is more acidic than extracellular fluid, with the result that bases cross the cell membrane and are trapped in the intracellular

compartment. One consequence of this relative partition is a higher V_d. After somatic death there is a sharp decrease in blood pH as a result of continuing cellular metabolism with carbon dioxide accumulation until available oxygen is exhausted and then there is anaerobic metabolism of glucose to lactic and pyruvic acids. In the minutes immediately following somatic death this very rapid fall in blood pH may cause redistribution of some drugs. There is some evidence that significant increases in blood morphine concentration occurring in the minutes after death are a result of the repartitioning of the drug consequent on pH changes.

The solid organs, which provide the most significant drug depots for postmortem drug redistribution, are those that combine a high drug concentration with a relatively large mass and an association with large blood vessels. The liver, the lungs, and the heart are the organs most responsible. Skeletal muscle, although amounting to about 30 kg of a 70-kg body, tends to have drug concentrations similar to or only a few fold greater than blood. Many drugs concentrate in liver at levels 50-fold or more than in blood. It was for this reason that liver was used historically for postmortem screening for drugs. Drug diffuses from the liver postmortem into the inferior vena cava and thence the right heart, superior vena cava, and contiguous neck and subclavian veins. In life, the lungs receive the entire blood flow from the right ventricle and therefore drug distribution into and accumulation in this tissue are very rapid. Compounds that specifically accumulate in the lungs are basic amines, for example, imipramine, amphetamines, methadone, and chlorpromazine. These exogenous basic amines are thought to be removed from the blood by the same carrier-mediated sodium-dependent transport systems that remove the endogenous amines 5-hydroxytryptamine and norepinephrine (noradrenaline) from the pulmonary circulation. For these drugs the ratio of lung tissue to blood concentration in life may be as high as 200 and this very large gradient provides the basis for postmortem drug redistribution into the pulmonary vessels and thence the cardiac chambers, as well as directly into the adjacent thoracic aorta. Cardioactive drugs, such as diltiazem, a calcium-channel blocker, and digoxin, are concentrated in the myocardium in life and after death show postmortem redistribution from the myocardium into cardiac blood. The endothelial cells of capillaries heavily concentrate some drugs such as phenobarbital. Postmortem release of drugs from endothelial cells into the blood is potentially very rapid. Certainly endothelial cells are shed into the blood during the first day postmortem.

Postmortem drug redistribution from solid organs into the blood occurs by passive diffusion, as described by Fick's first law of diffusion, which states that the rate of diffusion is proportional to the concentration gradient across the diffusion barrier. Although drugs diffuse most readily along the vascular tree within the blood itself, anatomical structures such as the diaphragm and the wall of the aorta do not in practice provide major diffusion barriers. Diffusion is temperature-dependent but refrigeration of the body is not a significant factor in the early postmortem period since it typically requires 18 h or more for the core body temperature to fall to that of the environment, and drug redistribution is well underway within hours of death. However, refrigeration will slow the rate of continuing drug redistribution if autopsy is delayed for days, although this is not of practical significance. Diffusion is time-dependent also, and empirical studies on cadavers with repeated blood sampling over many hours shows increasingly dramatic rises in blood drug concentrations.

Movement of drug within the blood is not only a result of diffusion since there is also natural postmortem movement of blood within the vessels providing some physical transport of drugs. These postmortem movements of blood are associated with pressure changes resulting from rigor mortis and putrefactive gas formation. The extent of this postmortem blood flux is also influenced by the degree of fluidity of the blood in the individual case. Following death there is loss of vascular tone in the arterial tree so that blood pools in the small peripheral vessels with a relative emptying of the larger arteries. During the first 24 h postmortem there is reflux of blood from the heart into the superior vena cava and the associated neck veins as a consequence of rigor mortis involving the heart muscle. With the increase in intraabdominal pressure accompanying early putrefaction, there is blood reflux from the abdominal aorta into the thoracic aorta, from the inferior vena cava into the right atrium and contiguous superior vena cava, and reflux from the left cardiac chambers into pulmonary veins. With the resolution of rigor mortis, which is the result of muscle putrefaction, the heart chambers are emptied of blood and there is flow into peripheral arteries with associated slight movements of venous blood. Gravitational phenomena related to body position and the tendency of blood movements to occur along the most linear natural anatomical trajectories are additional features that cause the pattern and extent of blood flux to be highly variable from case to case. In general, femoral venous blood can be expected to be influenced least by the postmortem movement and mixing of blood.

Empirical observations on drug-poisoning fatalities as well as experimental small-animal models have shown that there is a common general pattern of

postmortem drug redistribution into blood. Lowest drug concentrations are found in blood from peripheral veins such as the subclavian and femoral veins. High drug concentrations are found in blood samples from the aorta, the superior vena cava, and the cardiac chambers, and the highest drug concentrations are found in the pulmonary vein and the suprarenal portion of the inferior vena cava. The latter two vessels drain blood from the lungs and the liver respectively. Thus, the lowest drug concentrations are found in blood samples from sites distant from the torso, which contains the organs in which drugs are most heavily concentrated, while blood samples from the heart or major vessels of the torso have much higher drug concentrations because of their proximity to these organs. This is not to say that the drug concentration in blood from peripheral sites – such as the femoral vein, simply because it is the lowest concentration – is unchanged from the time of death. Rather the drug concentration in peripheral blood is the closest available approximation to the drug concentration in blood at the time of death, but even so may be two- or threefold of that concentration. The difference in drug concentration between torso samples and peripheral venous blood samples is commonly several-fold and occasionally 10- or 20-fold. The preferred autopsy blood-sampling site for toxicological analysis is the femoral vein or the contiguous external iliac vein. Empirical cadaver studies suggest that the subclavian vein, although a peripheral venous site, is less reliable.

Postmortem drug redistribution accounts for the commonly observed fact that drug concentrations in blood vary significantly between blood samples taken at the same time from different anatomical sites in the one corpse. Overall drug concentrations in all blood samples postmortem increase with postmortem interval but the changes are most marked in torso blood samples. Consequently, the between-sample variability in drug concentration increases with postmortem interval. Although drug concentrations in peripheral venous blood, particularly femoral venous blood, increase least in the postmortem interval, they still do not represent precisely the drug concentration at the time of death but rather the best approximation available. Femoral venous blood is the best available postmortem blood sample, but is the best of a bad lot.

Some variability in drug concentrations between blood-sampling sites in cases of drug overdose is seen in life. During drug absorption, there is distribution of the drug from the blood to the tissues and this distribution phase lasts from 30 min to 2 h for most drugs. During this period there can be a sizeable difference between arterial and venous drug concentrations and this may be reflected in site differences in postmortem blood drug concentrations where a person has died during the absorptive phase. In both animal models and human case studies of drug overdose, drug concentrations in arterial blood are sometimes as much as twice that of venous blood. This phenomenon may be a contributory factor in causing the postmortem drug concentration differences seen in acute drug overdose deaths, but it has a relatively minor impact when contrasted with the phenomenon of postmortem drug redistribution.

Postmortem drug analyses are performed on whole blood because postmortem blood clotting and red cell lysis makes it impossible to obtain a plasma sample, the usual matrix for drug analyses in the living. Within an hour or less of death, blood clotting is initiated throughout the vascular tree and, at the same time, clot lysis is initiated. The two processes occur simultaneously and the effectiveness of the clot lysis will determine whether the blood at autopsy is clotted, or completely fluid, or partly clotted and partly fluid. As a result the amount of blood clot present in a postmortem blood sample varies from body to body, and from site to site within the same body. When fibrin clot is present it always entraps large numbers of erythrocytes, so that the clot is relatively red-cell-rich. For drugs with an unequal distribution between erythrocytes and serum, the proportion of red cells and blood clot in a postmortem blood sample submitted for analysis may influence the drug concentration. For most drugs this is not an important factor in practice. For some drugs, such as chloroquine, which has an erythrocyte to serum drug concentration ratio of 32:1, the erythrocyte content of the postmortem blood sample might dramatically affect the drug concentration. The blood obtained from limb vessels is most likely to be fluid and largely devoid of clots, reflecting the approximately inverse relationship between the endothelial-derived fibrinolytic activity and the diameter of the vessel from which the blood was obtained. The uncoagulable fluid blood often, but not universally, present in limb veins provides as homogeneous a sample for analysis as can be hoped for. Thus far there is no proven correlation between the differences in hemoglobin concentration of postmortem blood samples and the differences in the concentrations of drugs detected.

Stomach Contents

Unabsorbed alcohol and drugs present in the stomach at the time of death passively diffuse into surrounding tissues, organs, and blood vessels in the postmortem period. Direct diffusion of alcohol, drugs, and poisons from the stomach contents through the stomach

wall, diaphragm, and blood vessel walls to contaminate blood in the cardiac chambers and surrounding great vessels can be a significant problem, particularly with respect to alcohol analysis. It is a further reason to avoid sampling torso blood for the quantitative analysis of alcohol and drugs. Unabsorbed drug in the stomach also diffuses into the adjacent liver. The gastric contact area on the inferior surface of the liver is centered on the left lobe. There is both empirical and experimental evidence that drug levels in the left lobe of the liver may rise significantly postmortem as a consequence of drug diffusion from gastric contents. For this reason a liver sample for analysis should be taken from deep within the right lobe, the site most protected from this effect by distance and tissue mass.

A common autopsy finding is contamination of the airways by gastric contents as a result of agonal vomiting or passive postmortem reflux following relaxation of the esophageal sphincter at death. Any drugs or alcohol present in this material contaminating the airways diffuse readily into the blood within the cardiac chamber and the great vessels of the heart, including the pulmonary vessels, superior vena cava, and aorta. Spurious analytic results for alcohol and drugs resulting from this postmortem artifact are readily avoided by taking the blood sample from a peripheral vein.

Bacterial Activity

The bacteria, which break down the body tissues during decomposition, are also able to degrade some drugs. As a result the concentrations of susceptible drugs in blood may decrease during the postmortem interval. Drug lability to bacterial degradation is related to the presence of one of three chemical structures in the drug. Oxygen bonded to nitrogen but not to carbon or sulfur renders a drug labile. This occurs with nitro-groups bonded to either an aromatic nucleus or to a nonaromatic structure and also occurs with oximes and with *N*-oxide structures, e.g., chlordiazepoxide. A second vulnerable structure is sulfur in a chain bonded as a thiono-group (C=S, P=S), e.g., malathion. The third vulnerable group of compounds is the aminophenols, which have OH and NH_2 groups on the same aryl nucleus. Structures possessing a primary arylamine group, which are not phenolic or are phenolic but do not possess such an amine group, or have a substituted amine group, for example acetaminophen (paracetamol), are all stable. The stability of drugs generally reflects the stability of chemical structures in which carbon bonds with oxygen and nitrogen, nitrogen bonds with hydrogen, and sulfur bonds with oxygen. Sulfur forming part of a heterocyclic ring causes some instability to putrefaction, e.g., dothiepin and the phenothiazines. The observation that the degradation of these latter drugs is variable suggests that the bacteria capable of degrading them are less widely encountered than those capable of breaking down the other labile chemical structures. While the lability or stability of a drug to putrefactive bacterial degradation may be generally inferred from its chemical structure, anomalies have been observed, for example thiopental would be expected to be labile but is stable, and bendrofluazide would be expected to be stable but is unstable. Furthermore, a drug with a high V_d and a labile chemical structure can be expected to show postmortem redistribution effects, with increases in blood drug concentration, as well as later putrefactive degradation, with decreases in blood drug concentration, both of which are anatomical site- and time-variable.

Ethanol is formed postmortem by microbial action. A wide variety of bacteria normally present in the gut, and responsible for putrefaction, can generate ethyl alcohol in blood and other tissues. Also, yeasts, such as *Candida albicans*, may be responsible for postmortem alcohol production. Ethanol synthesis takes place by a pathway opposite to that of ethanol catabolism in the living body. The necessary alcohol dehydrogenase and acetaldehyde dehydrogenase enzymes are provided by the microorganisms while the carbohydrate substrates glucose and lactate are present in blood and tissues. The anatomically isolated position of the vitreous humor of the eye protects it from bacterial putrefaction. For this reason analysis of vitreous humor is useful to corroborate a postmortem blood alcohol and assist in distinguishing antemortem intoxication from postmortem alcohol production. Urine is similarly useful because it normally contains little or no substrate for bacterial conversion into ethanol, except as a consequence of some pathological abnormality, particularly diabetes mellitus.

Autopsy Sampling

In practice postmortem blood samples for quantitative toxicological analyses should be obtained from the femoral vein or the contiguous external iliac vein. Ideally, the sample should be obtained as soon as possible after death. Obtaining such a sample at the scene of death is good practice. If the sample is obtained at autopsy then it should be taken at the very start of the dissection. The femoral vein can be exposed through an incision in the groin, or the external iliac vein exposed through the normal autopsy abdominal incision. The blood sample should be obtained by a needle and syringe and not by severing

the vessel and allowing the blood to flow into an open container, or to pool in the tissues or pelvis before collection. Prior to taking the sample the vessel must be ligated or clamped proximally, to avoid drawing blood from the immediately contiguous common iliac vein and the inferior vena cava. When a large volume of postmortem blood sample is needed for drug screening, that is to say qualitative rather than quantitative analysis, the sample may be obtained from anywhere. Best practice is to obtain a large volume of torso blood sample for qualitative analysis and a necessarily smaller volume of femoral venous blood for subsequent quantitative analysis. Sequestered hematomas, such as intracerebral hematomas and subdural hematomas, can be analyzed for alcohol and drugs, and give an indication of their presence in the body at the time the hemorrhage occurred – information that is useful if there has been a significant survival time. All blood samples should be labeled with their specific anatomical site of origin. Blood specimens should be preserved by adding 2% wt/vol sodium fluoride to the container. This inhibits microorganism production of ethanol, conversion of cocaine to ecgonine methyl ester by cholinesterases, and enzymatic loss of other esters such as 6-acetylmorphine. Preservatives are generally not required for other specimens.

For the purpose of corroborating a blood alcohol analysis on femoral venous blood, a sample of vitreous humor from the eye together with a urine sample, if the bladder contains urine, should always be taken. Urine is obtained directly from the unopened bladder by needle and syringe. Vitreous humor is obtained by direct aspiration from each eye using a small-volume syringe and a needle inserted adjacent to the outer canthus at an angle of 45° to the sagittal plane. Gentle suction avoids contamination with retinal fragments and typically produces 2–3 ml of slightly viscous fluid from each eye.

If stomach contents are retained for the purposes of assessing whether a death has occurred acutely following a drug overdose then the sample is best obtained last during the autopsy procedure, to avoid the possibility of contaminating other samples. The volume of the gastric contents should be measured at autopsy and a representative aliquot or the entire sample submitted for analysis. If the analytical laboratory has a preference for liver tissue analysis then the sample should be obtained from deep within the right lobe to minimize diffusional effects from stomach contents. Bile is easily collected by needle and syringe from the gallbladder at autopsy and, historically, has been most often used in the determination of opiates in general and morphine in particular. Many drugs are concentrated in bile.

In addition to liver, the tissues commonly collected for postmortem toxicological analysis are lung, brain, and kidneys. Lung tissue is a useful sample where there has been inhalation of volatile substances such as toluene. Brain, as a result of its high fat content, tends to accumulate lipophilic substances such as chlorinated hydrocarbons and other organic volatiles and should be sampled when these toxic compounds are suspected. Where heavy-metal poisoning is suspected, the kidney is a useful sample because heavy metals are concentrated there. Hair and fingernails are also the specimens of choice in assessing chronic heavy-metal poisoning such as from arsenic, mercury, and lead. Keratin is present in large amounts in hair and nails and is a rich source of cysteine. Heavy metals bind to sulfhydryl groups on the cysteine molecule to form a covalent complex. Numerous therapeutic drugs as well as drugs of abuse have been detected in head hair. Segmental analysis of occipital head hair, which grows at a rate of about 1 cm per month, can be used to assess chronic drug usage.

When the body is decomposed, has been embalmed, or is a case of exhumation, so that no blood sample is available, then the generally favored tissue sample for drug analysis is skeletal muscle. The sample is usually taken from the anterior thigh as a matter of convenience because this is the most readily accessible large muscle bulk in a supine cadaver. Any limb muscle would suffice but torso muscle, particularly the psoas, should be avoided because of the risk of postmortem drug diffusion from the stomach contents and viscera.

Where a body is maggot-infested the samples taken for toxicological analysis should include the maggots. Drugs present in a corpse are ingested by the maggots and sometimes concentrated within them. Furthermore, the maggots can be technically easier to analyze than the decomposing tissue of the corpse, which contains many putrefactive compounds that interfere with chromatographic analysis. Maggots can be killed with hot water, dried with paper towelling, and stored frozen. Drugs may also be detectable in the empty pupal cases left on the corpse after the flies have emerged.

All specimens, appropriately labeled, should be stored, sealed at 4 °C, and then transferred to –20 °C if long-term storage is necessary.

See Also

Autopsy, Findings: Postmortem Drug Measurements, Interpretation of; **Drug-Induced Injury, Accidental and Iatrogenic**; **Pharmacology of Legal and Illicit Drugs**; **Postmortem Changes:** Electrolyte Disturbances

Further Reading

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Organic Toxins

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Introduction

Previous articles have reviewed various applications of toxicology used in forensic and legal medicine with a focus on synthetic and semisynthetic drugs. Naturally occurring toxic substances or organic toxins are more frequently encountered in forensic cases than might initially be considered and are often regionally specific depending on the availability of the plant, animal, or other sources of such substances. Ethanol and carbon monoxide (CO) are some of the most common substances, and are considered elsewhere in this encyclopedia. Other organic toxins include hydrogen cyanide, methanol, hydrocarbons, and other volatile substances, plant poisons, and animal poisons including venoms.

It would be impossible to list, let alone discuss, all organic toxins that come under this classification. Consequently, this article outlines some of the more significant organic-based poisons not covered elsewhere and illustrates their relevance to forensic and legal medicine.

Volatile Substances

Those toxins of a volatile nature of most importance are listed in **Table 1**.

Alcohol

Alcohol (as ethanol) is produced by the fermentation of cereals and fruits, and is a common substance produced in decomposing bodies. When present in specimens obtained from putrefying bodies, it is often difficult to establish whether any ethanol was present at the time of death since up to at least 0.2 g per 100 ml can be produced in the right circumstances. When available, vitreous humor can be used to determine the respective likelihood of the source of ethanol since it is much more protected from bacterial contamination postmortem.

Carbon Dioxide and Carbon Monoxide

These gases are important asphyxiants in forensic cases. When persons are exposed to CO, its presence can be determined spectrophotometrically as a complex bound to hemoglobin. The percentage bound to hemoglobin (% saturation) is a relatively stable adduct blocking the ability of hemoglobin to store and hence mobilize oxygen. Percent saturations over 20% are dangerous, while percent saturations over 50% are often fatal. In medicolegal cases, it is most often associated with death by suicide from exhaust gases from motor vehicles, or from inhalation of gases in fires. In fires, it is toxic at a lower saturation (<30%) due to the presence of other asphyxiant gases (carbon dioxide, hydrogen cyanide, and hydrogen chloride).

In some situations of apparent CO death from inhalation of motor vehicle gases, CO may not be present. Motor vehicles fitted with emission controls will often not produce significant CO once the engine is warm; rather the large amounts of carbon dioxide present are sufficient to cause death from simple asphyxiation (lack of oxygen) and/or metabolic acidosis, particularly if ventilation is poor. CO should always be considered in "strange" indoor deaths if fuel

Table 1 Important volatile organic toxins encountered in forensic medicine

Organic toxin	*Source*
Ethanol (alcohol)	Fermentation of specimens, decomposing bodies, numerous alcoholic beverages, methylated spirit
Carbon dioxide	Automobiles and other internal combustion engines, compressed gas
Carbon monoxide	Automobiles and other internal combustion engines, fires
Cyanide (hydrogen and inorganic salts)	Cyanotic bacteria, gases from fires and cyanide salts
Methanol	Alcoholic drinks, metabolism of pectins, industrial solvent
Other volatile substances	Methane (natural gas), propane (liquefied propane gas), butane (lighter fluids), automotive fuels, aviation fuels, solvents, and miscellaneous gases

heaters or open fireplaces are operating, particularly if ventilation is poor.

CO can be easily measured by differential spectrophotometry by virtue of the unique spectrum produced by the adduct with hemoglobin. A number of commercial instruments are available to measure CO. In postmortem specimens, putrefaction or otherwise altered blood can best be measured by gas chromatography either directly or by conversion to methane. While carbon dioxide can be measured by chromatographic means, given its presence in air there can be no value in measuring this gas in specimens, particularly in the postmortem situation.

Cyanide

This substance is highly toxic and should always be considered as a potential poison in unsolved cases, particularly in deaths of persons with occupations associated with laboratories (such as chemists and biochemists). Inorganic salts (potassium and sodium salts) have electroplating and metallurgical applications, while the gas has been used as a fumigant and insecticide as well as a warfare agent.

In forensic cases, the gas (hydrogen cyanide) appears most commonly in persons exposed to fires, particularly those that involve burning plastics. When this occurs, toxic blood concentrations may be as low as $0.5\,mg\,l^{-1}$. Fatal exposure to inorganic salts generally leads to much higher blood concentrations of cyanide, often well over $2\,mg\,l^{-1}$. Cyanide will be gradually "lost" in specimens stored for prolonged periods. This occurs through both volatilization and inactivation by tissues. Cyanide can be produced in blood and other specimens by the action of cyanogenic bacteria. Therefore, it is recommended to analyze specimens as soon as possible after collection or to store specimens frozen at –60 °C until analysis.

Methanol

This poisonous alcohol is fortunately rare in forensic cases due to its relative scarcity in many parts of the world. However, if consumed, it is very toxic at doses over 10 ml, largely due to its metabolism to formaldehyde and formic acid. Blood concentrations vary widely and will of course depend on the time from ingestion; however, fatal concentrations are often over $100\,mg\,l^{-1}$ (0.01%). Trace amounts of methanol are produced following the metabolism of pectins contained in fruit and it is present in trace amounts in most alcoholic beverages. In this situation, blood concentrations are usually much less than $100\,mg\,l^{-1}$. The metabolism of methanol is inhibited by co-consumption of ethanol. Consequently, methanol may accumulate to toxic levels in alcoholics whose blood alcohol concentration is continuously above 0.02%.

Methanol is measured by techniques similar to those of ethanol.

Other Volatile Substances

A number of other volatile substances are encountered in forensic cases. These usually occur through abuse of volatile substances and consist of hydrocarbons such as butane from lighter fluid refills, liquefied propane gas (LPG), automotive and aviation fuels, and a variety of domestic and industrial solvents. Abuse occurs by inhalation of the substance contained in a plastic bag or similar container, or through direct injection into the oral cavity through a pressurized can. Inhalation of these central nervous system depressants can lead to anoxia, heart rhythm abnormalities, or even a direct effect on the vagal reflex, leading to a cardiorespiratory arrest. Long-term use can lead to cognitive deficits and adverse behavioral changes. Occasionally volatile substances can be detected in accidental exposures through inhalation of fumes from fires, and explosions, including aviation incidents.

Toxicologically these substances are detected by use of headspace gas chromatographic techniques similar to that of ethanol. When exposure to volatile substances is suspected it is advised to provide a sample of lung fluid, or better, a whole tied-off lung. This provides a better opportunity for detection of substances that can readily dissipate on storage.

Plant-Based Toxins

Nicotine and Related Alkaloids

Nicotine is arguably the most common plant-based poison used in the community. While its main use is in tobacco-related products, it has also been used as an insecticide (as solutions of sulfate salt). A number of proprietary products now contain nicotine to wean people off tobacco, including chewing gum, nasal sprays, and transdermal patches. Nicotine is highly toxic, causing stimulation of the parasympathetic nervous system. Toxic doses cause pinpoint pupils, vomiting, excessive salivation and sweating, tachycardia, hypertension, and eventually convulsions and cardiorespiratory failure. It is easily absorbed orally, through inhalation of aerosols or smoke, or through dermal exposure. Consequently, significant exposure can be readily attained. Poisoning cases are still seen in tobacco workers who absorb the alkaloid through their skin, persons who inhale aerosols from spraying crops with nicotine solution, persons

using multiple skin patches, and in children who eat nicotine-containing gum or patches.

A number of related substances are known that produce similar effects to nicotine by mimicking the effects of acetylcholine. These include muscarine from ingestion of *Amanita muscaria* mushrooms, atropine, and hyoscine (scopolamine) found in deadly nightshade (*Atropa belladonna*) and in many *Datura* spp. (or *Brugsmansia* spp.) (angel's trumpets, thorn apple), and lobeline found in lobelia plants.

The ancient poisonous weed hemlock (*Coniine maculatum*) is a relatively widespread biennial herb that contains a chemically related substance to nicotine, known as coniceine. This substance (and related substances in the plant) produces similar effects to nicotine at low doses (i.e., it stimulates the autonomic nervous system), but it causes paralysis at higher doses, resembling the effects of a narcotic.

Many deaths have been reported from these nicotine-like alkaloids. Most of the substances listed here are measurable by modern gas chromatographic techniques. Extraction from alkalinized blood and chromatography on a nonpolar to medium polar column will achieve adequate detection limits for nicotine, atropine, hyoscine, and coniceine.

Digitalis Glycosides

Digitalis glycoside digoxin and digitoxin are potent cardiotonics found in *Digitalis* spp. (foxglove). Digoxin is available in tablet form and is prescribed to persons with congestive heart failure and atrial fibrillation. The glycosides are very toxic if blood concentrations exceed about $5\,\mu g\,l^{-1}$, so regular therapeutic drug monitoring is necessary. Other plants have substances that behave similarly to digoxin. Oleander is a free-flowering bush widely grown in eastern Australia, known botanically as *Nerium oleander*. Another plant, sometimes known as yellow oleander, is *Thevetia peruviana*. Both plants belong to the family Apocynaceae. Oleander contains a toxic substance that acts as a cardiac glycoside, of which oleandrin is the main active chemical. The content of oleandrin in dried leaves is about 0.13%, although this toxic substance is also found in the stems and flowers. The toxic activity in these plants varies from season to season. The toxic principles in oleander are not destroyed by heat, such as during boiling. Oleandrin has a similar activity on the human heart as digitalis glycosides. Digoxin and oleandrin act to increase heart actions (mainly force of contraction), and in higher doses affect the ability of the heart to function properly. Adverse effects include nausea, vomiting, visual disturbances (color hallucinations), headache, cardiovascular disturbances, salivation, abdominal pain, mydriasis (dilated pupils), and peripheral neuritis.

Death can occur with serious poisoning. Death is associated with abnormal heart rhythm leading to cardiovascular collapse.

Immunoassay screening assays used to monitor digoxin have substantial cross-reactivity with oleandrin.

Once exposure to oleander poisoning has been determined, the administration of antibodies to digitalis glycosides (Digibind) will reverse the effects of toxic substances in oleander.

Psilocybin

One of the more common poisonings in certain parts of the world is exposure to "magic mushrooms." Psilocybin is found in *Psilocybe* spp. and in some *Panelous* and *Concybe* genera. Psilocybin is converted metabolically to psilocin, the main active indole alkaloid. This substance interacts with serotonin ($5HT_{1A}$ and $5HT_{2C}$) and norepinephrine (noradrenaline) receptors in the brain. Psilocin causes anxiety, disorientation, depersonalization, psychosis, and hallucinations. Other adverse effects include severe nausea, vomiting, cardiovascular side-effects, hyperthermia, dilated pupils, and convulsions. These effects usually last for about 2 h and can be extremely intense and frightening.

Psilocin can be measured by high-performance liquid chromatography with electrochemical detection, gas chromatography–mass spectrometry, or liquid chromatography–mass spectrometry (LC-MS). If urine is used, conjugates should be hydrolyzed first to increase detectable alkaloid.

Ricin

One of the most toxic plant substances is the toxalbumins found in the castor-oil plant (*Ricinus communis*), *Jatropha multifida* (Jatropha fruit) and other Jatropha genera (active: ricin), and rosary pea (*Abrus precatorius*) (active: abrin). These lectins, consisting of two polypeptide chains, bind to intestinal cell walls and inhibit ribosomal protein synthesis. Ingestion of castor-oil seeds is a relatively common childhood poisoning episode, although seeds without broken seed coats are much less toxic. Symptoms include hypotension, severe gastrointestinal pain, acute pulmonary edema (if inhaled), and tissue necrosis. Kidney and liver failure is common. Adverse symptoms are often delayed for one to several days. A number of deaths are known from ingestion of these toxins. Antidotes are not known. A number of other lectins from other plant species are also toxic. Purified ricin from the castor-oil plant has been implicated in attempted poisonings and terrorist

activities. Its analysis has been largely restricted to immunological procedures.

There is a multitude of other plant-based poisons, some of which are listed in Table 2. Of particular note are cocaine, tetrahydrocannabinol (*Cannabis sativa*), and morphine (opium poppy). These common plant poisons are covered elsewhere.

Animal-Based Toxins

The variety of animal toxins is enormous. Venomous or poisonous animals are ubiquitous and widely distributed throughout the animal kingdom and found in almost all continents and oceans. Animals can either secrete toxins (venomous) or be toxic if consumed (poisonous).

Table 3 provides a short list of such land and marine animals and the toxic substances associated with their toxic actions.

In the seas and oceans one of the most common forms of mortality is envenomation by one of the numerous forms of poisonous jellyfish. Many of the toxins used are unknown but are believed to be mainly polypeptides that cause ion channel disturbances in smooth and skeletal muscle as well as serious immune responses. One of the more unusual forms is the Irukandji syndrome, in which many of the symptoms resemble catecholamine toxicity such as anxiety, sweating, piloerection, hypertension, and tachycardia. Pathologically, there are often few signs of envenomation.

Another relatively common source of mortality is ingestion of toxins contained in mollusks, crab flesh, and other related organisms. This is known as paralytic shellfish poisoning (PSP) or neurotoxic shellfish poisoning (NSP). These toxins include saxitoxin, palytoxin, and others such as tetrodotoxin. They all act to interfere with ion permeability in membranes.

A form of fish poisoning that is a significant public health issue is that of ciguatera poisoning. This is caused by ingestion of the ciguatoxins that accumulate in the food chain in warm-water fish. While rarely fatal, they have the potential to be so by their effect on sodium ion channels in nerves. These toxins are high-molecular-weight heat-stable polyethers with

Table 2 Important plant-derived organic toxins encountered in forensic medicine

Organic toxin	*Source*
Cocaine	*Erythroxylon coca*, and certain pharmaceutical preparations
Coniine and related alkaloids (coniceine)	*Conium maculatum* (hemlock)
Digitalis-like glycosides	Digoxin (and digitoxin), foxglove plant (*Digitalis* spp.), cane toad (*Bufo marinus*), oleander (*Nerium oleander*), yellow oleander (*Thevetia peruviana*)
Ibogaine	*Tabernanthe iboga*, licit and illicit sources as hallucinogen and for treatment of addictive behavior
Morphine and related alkaloids	Opium poppy, pharmaceutical preparations, heroin, codeine
Nicotine	Tobacco products, patches and other pharmaceutical preparations, insecticide products
Ricin and abrin	*Ricin communis*, castor-oil plant, industrially used in immunology, *Jatropha* spp., *Abrus* spp.
Psilocybin	*Psilocybe* spp., *Panelous* spp., *Concybe* spp. of mushrooms
Scopolamine	*Hyoscyamus niger* (henbane), *Datura stromonium* (jimsonweed), and other plants
Strychnine	*Strychnos nux vomica*, rodenticides

Table 3 Important animal-derived organic toxins encountered in forensic medicine

Type of poisoning or envenomation	*Toxin and source*
Jellyfish envenomations	Wide-ranging types of jellyfish can cause serious envenomation. Often caused by polypeptides, leading to abnormal sodium and calcium ion permeability, particularly in smooth muscle and heart; many toxins are not identified
Paralytic shellfish poisoning or neurotoxic shellfish poisoning	Saxitoxin, palytoxin, and other toxins found in bivalve mollusks, crab flesh and other marine species
Puffer fish poisoning, and related poisonings	Tetrodotoxins found in fugu (Japanese puffer fish). Tetrodotoxins are also used by the blue-ringed octopus, found in the skin of Central American frogs, the cutaneous glands of the Californian newt, in some marine fish with spiny fins, some shellfish, and many other marine species
Ciguatera poisoning	Ciguatoxins are found in larger tropical fish, leading to ''fish poisoning''
Snake, spider and scorpion bite envenomation	Largely protein-based substances or polypeptides leading to hemolytic, neurologic, renal, and cardiovascular abnormalities

a potency that is unlikely to allow ready analytical detection in victims.

Tetrodotoxin and related toxins (maculotoxins) are the main poison in puffer fishes, a delicacy of the Japanese, as well as in the blue-ringed octopus, the skin of Central American frogs, in the cutaneous glands of the Californian newt, in some marine fish with spiny fins, some shellfish, marine gastropods, and many other marine species. Symptoms of poisoning include nausea, vomiting, blurred vision, muscular weakness, and paralysis of respiratory muscles. Mortality is high from this toxin.

Many other marine animals can inflict serious envenomations or cause poisonings.

A number of toxins mentioned above can be detected by the use of microtiter radioimmunoassay or enzyme-linked immunosorbent assay tests using antibodies raised against the toxin. More recently, LC-MS has been used to identify toxins in both the organism and specimens taken from the victim.

Bee and wasp stings are prevalent through many parts of the world and are arguably one of the leading causes of death from envenomation, for example, *Hymenoptera* wasp stings. The sting of the common European honey bee *Apis mellifera* can cause anaphylactic reactions in susceptible persons. Anaphylaxis is potentially serious and can often lead to death. The risk is increased with multiple stings. Symptoms may range from local swelling and pruritus to marked edema leading to bronchospasm, dyspnea, and cardiorespiratory collapse.

Venomous snakes are a major cause of serious to fatal envenomation throughout much of the world, particularly the USA, Australia, and Asia. The large number of dangerous species precludes any detailed review here; rather the reader should refer to relevant texts.

Snake venoms are complex in nature, comprising chiefly proteins. These proteins are often enzymatic in nature, including proteolytic enzymes, thrombin-like enzymes, collagenases, phosphoesterases, and phospholipases. These proteins are capable of causing local and systemic tissue damage. In some species, polypeptides act on the postsynapse to block the effects of endogenous neurotransmitters (e.g., acetylcholine nicotinic receptors) and in others affect movement of ions through the sodium channel.

Venomous spiders and scorpions are another large and dangerous group of animals that inflict many serious and often fatal envenomations every year. These venoms are again often proteins or polypeptides in nature, although some exceptions exist. The measurement of tissue specimens for snake, spider, and scorpion venoms is largely restricted to immunological tests. In some countries, kits are available to allow the detection of toxins resulting from snakebite, or at least to exclude snakebites as a cause of death when there is little or no pathology, or the circumstances do not allow unequivocal proof of an envenomation.

See Also

Alcohol: Breath Alcohol Analysis; Blood and Body Fluid Analysis; Acute and Chronic Use, Postmortem Findings; **Carbon Monoxide Poisoning:** Clinical Findings, Sequelae In Survivors; Incidence and Findings at Postmortem; **Toxicology:** Methods of Analysis, Antemortem; Methods of Analysis, Postmortem

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Fire

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Introduction

Recent studies have concluded that house fires, which are more frequent than any other fires, cause fire-related injuries in 3–5% of fires and fire-related deaths in 1–2% of fires. In all international studies,

the rates of injury and death related to house fires are highest among minority and low-income populations. Children and the elderly represent a disproportionate percentage of fire victims. Victims under the age of 10 years or over the age of 70 years constitute most fire fatalities in all developed countries.

The rate of injuries is higher for fires that begin in bedrooms or living areas, that are started by smoking, defective electrical wiring, faulty or misused heaters, children or adults playing with fire, or that occur in very old houses. From various sources, cooking (1 in 3) and smoker's materials (1 in 5) seem to be the main sources of fire.

Most deaths in fire are attributed to a combination of smoke inhalation and burn injury. Moreover, half of the victims aged 18 years and older test positive for alcohol or other substances. These epidemiologic considerations lead to forensic guidelines for forensic doctors and crime-scene investigators faced with examinations of fire victims.

Etiology and Pathology of Fire Fatalities

A variety of factors may lead to fire fatalities. Most frequent are smoke inhalation and burn injury. In flame burns, there is actual contact between the body and the flame, with scorching of the skin progressing to charring. Flash burns are caused by initial ignition from flash fires that result from the sudden ignition or explosion of hydrocarbon fuels or fine-particulate material. Typically, the initial flash is of short duration, a few seconds at most. All exposed surfaces are burned uniformly. If the victim's clothing is ignited, a combination of flash and traditional flame burn occurs. Extremely high radiant-heat temperatures can cause burns in seconds. Air temperatures above 1500 °C will cause second-degree burns on bare skin in less than 10 ms.

The extent of the burn is indicated as a percentage of total body surface area affected by thermal injury. This is determined by the classic "rule of nine": the head (9% of body surface), the upper extremities (each 9%), the front of the trunk (18%), the back (18%), each lower extremity (18%), and the perineum (1%).

Burns are also described according to their characteristics as from superficial to full-thickness burns. They are classified as first-, second-, third-, or fourth-degree burns. In first-degree (superficial) burns, the skin is erythematous without blisters. The skin is intact, with some injury of the epidermic cells and dilated congested vessels in the dermis. Second-degree (partial-thickness) burns can be either superficial or deep. The external appearance is a moist, red, blistered lesion. There may be blistering. Destruction of the striatum granulosum and corneum, and edema at the dermal–epidermal layers are present. Deep second-degree burns show a complete disruption of the epidermis and destruction of the basal layer.

In third-degree (full-thickness) burns, there is coagulation necrosis of the epidermis and dermis with destruction of the dermal appendages. The extended lesions usually have a leather-like appearance. The lesions may be white, brown, or black. In fourth-degree burns, incinerating injuries extending deeper than the skin are present.

Both the size of the burn surface and the degree of burns, as well as the area in which the injury is inflicted, can play a direct role in the prognosis. Clothes worn by the burn victims can play a protective role but can also ignite and add more lesions if the clothes are highly flammable.

Toxic Gases and Death from Smoke Inhalation

Examination of victims who have died from smoke inhalation usually reveals soot in the nostrils and mouth as well as burns, and coating of the larynx, trachea, and bronchi at autopsy.

Thermal burns of the tracheobronchial tree are rare but hot air, whether dry or moist, can produce a rapidly fatal obstructive edema of the larynx. Moreover, the inhalation injuries of the lungs are frequently chemical injuries caused by combustion of toxic substances.

Absence of soot at external examination does not necessarily mean that the individual was dead before the fire started, since analysis of blood for carbon monoxide and hydrogen cyanide can reveal lethal levels.

Most victims of house fires die from carbon monoxide or at least are affected by it. In enclosed areas, in addition to carbon monoxide, hydrogen cyanide is responsible for death from smoke inhalation.

In 3857 fatalities of aviation accidents, occurring from 1991 to 1998, 41% were associated with fire, whereas 59% were not related to fire. There were fewer fire-related fatalities and associated accidents in the (carbon monoxide hemoglobin or COHb $\geq$ 10% and CN(−) $\geq 0.25\,\mu g\,ml^{-1}$) category than that in the (COHb $<$ 10% and CN(−) $< 0.25\,\mu g\,ml^{-1}$) category (Figure 1).

In house-fire victims, carbon monoxide and hydrogen cyanide, singly or combined, are probably not solely responsible for the deaths that occur in badly burned victims (a minority of fire victims). In fact, the significantly higher carboxyhemoglobin in unburned or scarcely burned victims (most fire victims)

Figure 1 Accidental death by fire: bodies of victims of the Concorde air crash in August 2001 retrieved in their seats with their belts fastened (note the body with shoes and seatbelt almost intact).

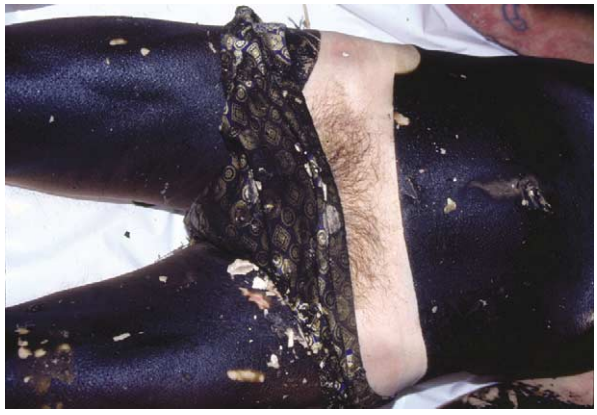

Figure 2 Smoke inhalation victim in a fire. The body does not show any major burns but its uncovered parts are darkened by soot. The skin appears white after partial removal of the underwear.

Figure 3 Smoke inhalation. The victim, poisoned by hot fumes, carbon monoxide, and hydrogen cyanide, had inhaled toxic fumes before her death. A percutaneous blood puncture allowed immediate blood analysis of her carbon monoxide and hydrogen cyanide concentrations.

indicates that carbon monoxide alone or combined with hydrogen cyanide plays a major role in the cause of death (Figure 2). Victims aged over 60 years often die either with carboxyhemoglobin concentrations below 60% or with a high concentration of hydrogen cyanide and a low concentration of carboxyhemoglobin. Carbon monoxide levels of 30% or 40% and even 20% may cause death if the victim suffers from an underlying disease such as severe coronary atherosclerosis.

The livor mortis, the muscles, and internal organs, as well as the blood, will have a cherry-red coloration but carboxyhemoglobin concentrations must be measured in blood sampled at autopsy.

If required, samples may be taken from the right ventricle at the scene of the fire and carbon monoxide levels rapidly obtained, following the guidelines of the US medical examiners. Results obtained for carbon monoxide concentration, using a detection method employed in emergency units, must be confirmed by reference methods. In a large series of data (from 1992 to 2002, in a population of 1.5 million inhabitants), in collaboration with a French national reference laboratory, first results have been confirmed by autopsy samples analyzed using a reference method (Figure 3). Their results give accurate answers to two questions: (1) Could death have occurred before the fire began? (2) Did the victims die from smoke inhalation?

A complete external examination of the body takes place near the scene of the fire. According to the results, criminal or fire investigations can immediately follow, keeping as many options open as possible for the police inquiry.

Figure 4 Accidental death by fire: a disabled man in bed was unable to escape from flames. Death was attributed to extensive burns in a living person at the time of fire. The victim's blood carbon monoxide concentration was high, but not lethal: his carboxyhemoglobin level was 32%.

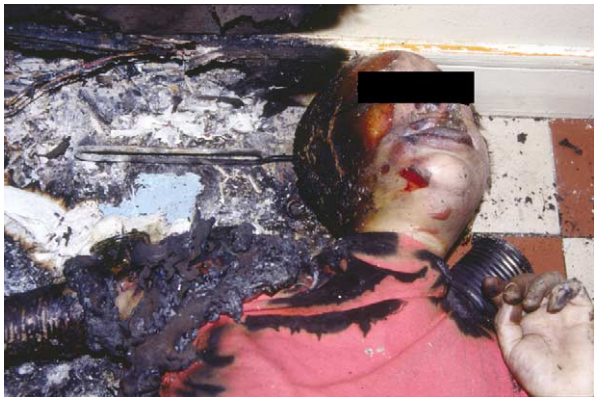

Figure 5 Accidental death by fire: aerosol burning with flash fire on the left side of the skull, face, neck, and shoulder.

Accidental Deaths by Fire

Accidental deaths by fire mostly involve children and elderly people playing with or using matches and lighters. Disabled adults are often involved in accidents with fire, as they may be unable to escape if a fire begins (Figure 4). Alcohol-related fires are also frequent in cases of alcoholic smokers (causing a fire in bed) or alcoholics using, for example, a fuel heater. Electric faults in old houses or renovated ones are also frequent. Electric faults may occur in industrial areas where high-voltage current is used. In car fires, often after a traffic accident, fire involves flammable hydrocarbon liquids. The flash point of hydrocarbons is the temperature at which sufficient fuel has evaporated to sustain a brief flash of fire, often started by an electrical device in the car. With hydrocarbon fuels, it is the vapors from evaporation that burn, not the fuel. When the vapor ignites, it raises the temperature of the hydrocarbon, causing increased and rapid evaporation of fuel and thus sustaining the fire. The flame in a flash fire moves out in all directions from the point of ignition. The temperature in flash fires from hydrocarbon fuels is 500–975 °C. Within a very short time of ignition, the oxygen level falls dramatically while carbon dioxide and carbon monoxide gases increase.

Fires in confined spaces such as a room can produce a phenomenon called a flashover, often involving a gas heater or device. Once a fire starts, it produces radiant heat, hot gases, and smoke. Initially, the fire and hot gases begin to heat the ceiling and adjacent upper walls and then objects in the lower portion of the room. In turn, the combustible materials in the room begin to give off flammable gases.

Adults may also be involved in accidents caused by the flammability of many aerosol cosmetics and household products; this can be attributed to the use of hydrocarbon propellants in combination with alcohol solvents. Products such as hairspray, deodorants, air fresheners, bug bombs, tire sealant, solvents, paints, and cleaners are propeled out of their aerosol gases, many of which contain propane, butane, isopropane, or isobutane. All these common products can generate dense, flammable vapors, creating a path for fire or explosion. When vapors spread throughout an enclosed space, they are subsequently ignited by an ignition source, and an explosion or flash fire may result. For example, a fatal case of burns by flash fire which caused the death of a 41-year-old woman when she used an air-freshener spray in a kitchen has been reported (Figure 5). The aerosol propellant gas consisted of a mixture of propane and butane and was ignited by the flame of a gas heater. Ignition resulted in a flash fire, extensively burning the woman.

Suicidal Deaths by Fire

Self-immolation is dramatic death by fire, and mainly occurs in adults between the ages of 20 and 40 years, who are suffering from significant mental disorders or have a history of alcohol or substance abuse. Immolation is rare. Suicide attempts usually pour a flammable liquid on themselves, generally gasoline, and set themselves on fire. The use of a flammable liquid is the most common method of immolation. The liquid container and matches or lighter are usually present at the scene. Victims should be examined for fingerprints. Generally, such suicide attempts present third-degree burns over most of their body, with the burns concentrated on the front part of

the body. In a large proportion of cases, death by immolation is not immediate and parasuicides may be taken to intensive-care burn units. A particular pattern of suicide can be evidenced by miniepidemics of suicide, influenced by local or national events or by mimicking the method of suicide. Clusters of suicide have been well documented in particular communities.

The medical examiner at the fire scene or the forensic pathologist at autopsy should retain portions of clothing for the analysis of volatile substances. The clothing should be placed in a container with a screw-top cap since volatile material may escape through a plastic bag. Soil from under the immolation victim may also be sampled by scientific police for analysis of the presence of volatile substances. In deaths caused by self-immolation outdoors or in a large room, as in accidental flash fires, burns are the main cause of death and low carbon monoxide concentrations are found. When immolation occurs in motor vehicles, the victims often present with both anterior burns (the back is protected by the car seat) and elevated carbon monoxide levels.

Homicidal Deaths and Fire

Analysis of inflammable substances to determine whether death has occurred before or after burning is of paramount importance for judicial inquiries. Carboxyhemoglobin saturation and paraffin hydrocarbons can be detected in the left-heart blood, when burning has been the cause of death. In contrast, very low carboxyhemoglobin saturation and the absence of hydrocarbons in the left-heart blood determine that the victim was set on fire after death, in an attempt to dissimulate that death had occurred before. Interpretation of accelerants in the blood of cadavers found in wreckage after fire is important to decide whether accelerants containing petroleum components had been used and whether the cadavers had been exposed to fire before or after death. Accelerants in the blood of cadavers found after fire are analyzed by a combination of gas chromatography and mass spectrometry (GC–MS) in cases where accelerants are suspected of being used to start a fire. In homicidal deaths, where victims are burned to hide the method of death, accelerants cannot be detected in the blood, soot cannot be found in the airways, and carboxyhemoglobin concentrations are not higher than those found in smokers. When soot cannot be detected by the naked eye in the airways of a victim found in the debris of a fire, when the carboxyhemoglobin concentration in the blood is no higher than in a smoker, the analysis of accelerants in the blood seems to be helpful in determining the cause of death and in confirming whether inflammables were used.

Identification of Fire Victims

Identification of deceased fire victims may be simple as, in many fire deaths, thermal injuries to the body are poor: death is caused by smoke inhalation. In such victims, identity can readily be established by personal identification (hair, teeth, tattoos, scars), photographs, and fingerprints. If a body is destroyed to such a degree that facial structures are mutilated and no fingerprints can be obtained, ante- and postmortem comparisons need to be made. It must be stressed that antemortem elements are fundamental for any reliable identification, using accurate comparison of various elements ante- and postmortem. Positive identification of victims is done by comparing ante- and postmortem criteria: scars and tattoos (Figure 6), jewelry, radiographs, dental radiographs, and DNA probes if necessary.

Dental identification is carried out by a forensic odontologist, using ante- and postmortem documents, dental charts, and X-rays of the jaws compared with the dental X-rays and charts of the individual who is believed to be the deceased. Radiography of jaws and teeth can provide one of the most reliable sources of information for comparison between ante- and postmortem conditions leading to definitive evidence in cases of identification since teeth and dental restorations are resistant to destruction by fire and are therefore very important in identification.

At autopsy, X-rays can be obtained to compare the postmortem X-rays with antemortem X-rays of the suspected individual, searching for a past fracture, an orthopedic material, and any bone pathology. Various radiographic examinations can provide a reliable source of comparison between ante- and postmortem conditions. Fractures, metal material, and peculiarities may be accurate criteria for postmortem identification.

Nowadays postmortem forensic identity uses polymerase chain reaction (PCR) to identify fire victims. To identify carbonized corpses and victims of large accidents, the analysis requires relatives of crash victims to give blood for analysis. DNA extracted from blood from the cardiac chamber or from any human remains of the decedent is analyzed using PCR and the results from all loci typing of the corpse are then compared with that of the alleged biological parents, which would confirm genetic compatibility.

Figure 6 Large blue tattoo on the skin of the trunk of a crash fire victim: Concorde air crash in August 2001.

Figure 7 A homeless alcoholic, found dead in a fire, was extremely drunk (blood ethanol concentration: 2.10 g l^{-1}).

Autopsy Findings in Fire Victims

Mortality is predominantly determined by the total body surface area burned and by inhalation injury. Inhalation burns can be diagnosed clinically and confirmed by means of autopsy: upper-airway, major-airway, and parenchymal burns. Major-airway burns are always seen in conjunction with either upper-airway or parenchymal injury. Extensive surface burns, parenchymal injury – and secondary pneumonia if the victims survive a short delay – all contribute to the significant mortality.

Fatal residential fires account for 10% of all accidental deaths in developed countries, with one-fourth of the deaths involving elderly people. Significantly more fires killing elderly people were caused by faulty or misused electrical items in the house, particularly electric blankets and heating devices. The fire-related fatality rate is highest among older persons. Alcohol is not a factor in fatal fires involving older adults. This differs from fatal fires involving the young and middle-aged adults. Ethanol or substance use may increase the risk of fire-related injury or death (Figure 7). From the records of all fatalities from fire reported to the US state medical examiner's office, blood assay results for ethanol were positive in 29.5% of fatalities of fire, and blood or urine assay results for substances of abuse were positive in 14.6% of fatalities. The most commonly detected illicit substances were cocaine, benzodiazepines, barbiturates, and cannabinoids. Forty percent of all the fatalities due to fire involved persons younger than 11 or older than 70. In contrast, 75% of drug-positive fatalities and 58% of ethanol-positive fatalities in fire involved persons between the ages of 21 and 50, suggesting that inebriation may impair the ability to escape from fire. Substance abusers in mid-life are at higher risk of injury or death in a fire.

A not uncommon external examination and autopsy finding is a skull fracture visible on the carbonized skull of a cremated corpse. Extensively burned bodies can show defects of the cranial bone. The question arises whether the fracture is caused by a gunshot wound. Reconstruction of the cranial remains with detached parts of the tabula externa can provide evidence that the suspicious defect can be classified as a heat-induced postmortem artifact.

Uncompleted cremations of bodies in fires are usually associated with fractures. In an intense fire, the external table of the cranium shows fissures or the sutures burst. Then the cranial vault is largely fractured, with the external table beginning to fragment: once the calvarium is burned away, a blackened brain is exposed. The facial bones are also calcined and disintegrate if the fire is still burning. Similarly, the skin of the anterior part of the trunk is fully burned and shows the anterior part of the ribs with the sternum and costal cartilage burned. The open thoracic and abdominal cavities expose blackened internal organs. After a longer delay, the exposed

ribs are further calcined. In regard to the extremities, the forearms are generally reduced to their proximal portions at the same time as the cranium is fractured. Similar phenomena take place on the legs.

The diagnosis of fractures needs to be carefully evaluated since real traumatic injuries may also be encountered. They involve frightened people jumping from a height to escape fire and victims injured or killed by a falling wall or furniture in an accidental fire, but may also involve homicide victims whom their perpetrators wish to destroy in a fire lit after their death.

See Also

Anthropology: Cremated Bones; **Body Recovery**; **Fire Investigation, Evidence Recovery**; **Injury, Fatal and Nonfatal:** Blunt Injury

Further Reading

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Drowning

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Circumstances of Death

The majority of drowning victims are young adults and children who die accidentally. Among adults, males predominate, and there is a strong association with alcohol consumption. Homicidal drowning is uncommon and requires physical disparity between the assailant and the victim or a victim incapacitated by disease, drink, or drugs, or a victim taken by surprise. Disposal of a corpse in water may be attempted where the victim has already been killed by another means. In some cultures, drowning is a common method of suicide. In suicidal drowning, some clothing may be left in a neat pile close to the water, weights may be tied to the body, or the pockets filled with stones. The hands or feet are sometimes tied together, and an examination of the ligatures will establish whether they could have been tied by the deceased. There may be concurrent use of other suicide methods, such as alcohol or drug overdose or slashing of the wrists. Persons attempting suicide by jumping from a bridge or a cliff into water may suffer injuries from impact against rocks or the water itself. Impact with the water can produce severe injuries, including fractures of the ribs, sternum, and thoracic spine, and lacerations of the heart and lungs. Diving into shallow water may result in an impact of the forehead against the bottom with resultant hyperextension of the head and loss of consciousness. Common autopsy findings are hemorrhage into the deep muscles of the neck, with or without associated fracture of the cervical vertebrae and primary-impact bruises and abrasions on the face or forehead.

The investigation of a death in a domestic bath includes consideration of drowning. It is critical to establish the position of the body as found, the level of the water, and whether the nose and mouth were truly under the water. Unconscious persons can drown in quite shallow water as long as it is sufficiently deep to cover the nose and mouth. Unconsciousness following an epileptic seizure, a cardiac arrhythmia arising on the basis of coronary artery disease, the consumption of alcohol or drugs, or a minor head injury from a fall may lead to drowning in the bath. Suicide by drowning in the bath is uncommon; victims are often found face down and partly or fully clothed. Homicidal drowning in the bath is rare. The domestic bathroom presents hazards other than drowning, such as electrocution and carbon monoxide poisoning from faulty heaters.

Most diving fatalities are recreational scuba divers and snorkelers. Scuba is an acronym for a self-contained underwater breathing apparatus, which allows the diver to reach depths not usually attained by skin divers. The commonest causes of death are drowning and barotrauma. If drowning is the terminal event, it is important to identify potential underlying causes: natural disease, trauma, fatigue, panic, equipment problems; environmental factors, such as current instability; and causes of a decreased level of consciousness, such as nitrogen narcosis, intoxication, oxygen toxicity seizure, and hypercapnia. Amongst snorkelers, unconsciousness due to breath-holding following hyperventilation, sometimes loosely termed "shallow-water blackout," is a common cause of drowning. In divers using compressed gases, pulmonary barotrauma and cerebral air gas embolism (extraalveolar air syndrome) represent the next largest group of fatalities after drowning. In a diver who makes an uncontrolled ascent without exhaling, the volume of lung gas expands as the ambient pressure falls, and if the diver does not exhale, air is forced from the alveoli into the pulmonary circulation, to the heart, and then into the cerebral circulation. The characteristic history is of the diver coming to the surface rapidly, crying out, and then losing consciousness within minutes.

Pathophysiology of Immersion

The normal physiological effects during head-out immersion in thermoneutral water are a result of the hydrostatic pressure of the water on the body. Overall, there is a significant increase in the work of breathing, but from a practical viewpoint there is little evidence that these changes cause difficulty in a healthy individual. However, a sudden fall in skin temperature resulting from sudden immersion in cold water initiates a group of cardiorespiratory reflexes known as the "cold-shock" response. The respiratory response is an initial gasp of 2–3 l in an adult, followed by uncontrollable hyperventilation, and a sensation of breathlessness. This makes swimming very difficult and is thought to be a major causative factor in the failure to swim effectively in cold water. Additionally, the maximum breath-holding time is reduced to less than approximately 10 s. As a result, in choppy or turbulent water, there is a significant chance of aspiration of water. The cardiovascular response is an immediate increase in heart rate and cardiac output, which may induce a cardiac arrhythmia, particularly in middle-aged or elderly people with cardiovascular disease. These factors explain why drowning may occur at short distances from safe refuge, even among good swimmers.

A diving response characterized by apnea, generalized marked peripheral vasoconstriction, and bradycardia is initiated by immersion of the face in cold water. The diving response found in humans is similar to that found in diving mammals but quantitatively less marked, with the cold-shock response predominating in the majority of normally clothed adults. Nevertheless, about 15% of people do show a profound reaction, and this percentage increases with the use of protective clothing, which prevents rapid cooling of the majority of the body but leaves the face exposed to the cold stimulus. In these circumstances, the competing influences of the cold-shock and diving response reflexes cause a variety of cardiac arrhythmias. Swimming appears to be a common activity that triggers an arrhythmia in individuals with familial long QT syndrome. This may account for some otherwise unexplained drowning in children and young adults. Molecular testing for the genetic abnormality can be performed on autopsy tissues, whether fresh or archived.

Prolonged immersion in cold water carries the risk of hypothermia, defined as a deep body temperature less than 35 °C. During head-out immersion in laboratory conditions, the deep body temperature of the average adult wearing outdoor clothing falls to 35 °C after 1 h in water at 5 °C, after 2 h in water at 10 °C, and after 3–6 h in water at 15 °C. However, because of the rich supply of blood vessels to the scalp that do not vasoconstrict in the cold, heat loss from the unprotected head may be enhanced in open water by forced convection and evaporation, thus increasing the rate of body cooling considerably. As core temperature decreases to less than 34 °C, consciousness becomes impaired and aspiration of water is likely to occur. Cardiac arrest from ventricular fibrillation may occur at deep body temperatures less than 28 °C and asystole at 24–26 °C.

Pathophysiology of Drowning

Drowning was originally conceived as suffocation due to the mechanical obstruction of the airways by liquid. Animal models of drowning, studied during the 1930s, suggested that drowning induced significant fluid shifts and electrolyte abnormalities that were dependent on the osmolarity of the fluid that was aspirated. Subsequent studies of human drowning fatalities and survivors suggested that electrolyte abnormalities were not so great. Consequently, the relative importance of mechanical airways obstruction and fluid and electrolyte shifts in the pathophysiology of human drowning deaths is unclear.

After inhaled water enters the alveolar spaces of the lungs, fluid and electrolyte shifts should occur along

osmotic and concentration gradients between the alveolar fluid and the blood. Fresh water is hypotonic and hyponatremic relative to blood, with the result that the inhalation of fresh water leads to movement of water from the alveoli into the blood and of sodium from the blood into the alveoli. The result is hemodilution, hypervolemia, hyponatremia, and hemolysis with associated hyperkalemia. By contrast, sea water, which is very hypertonic relative to blood, results in water movement from blood into the alveoli and movement of sodium, chloride, and magnesium from the alveoli into the blood. Consequently, there is hemoconcentration, hypovolemia, and hypernatremia.

Both fresh water and saltwater damage alveoli, destroy surfactant, and induce pulmonary edema with the transudation of protein-rich fluid into the alveolar spaces. There is decreased lung compliance and ventilation–perfusion mismatch so that blood flows through underventilated portions of the lung. The result is noncardiogenic pulmonary edema and hypoxia with secondary metabolic acidosis. It is these general effects of aspiration of water, rather than fluid and electrolyte shifts, that appear to dominate the pathophysiology of human drowning when contrasted with animal models.

The description of the various phases of drowning is based on animal experiments in which the animals were completely submerged and unable to break the surface. The initial submersion is followed by an immediate struggle and sometimes inhalation of water. Breath-holding lasts until carbon dioxide accumulation stimulates respiration, resulting in the inhalation of water, gulping of water, coughing, and vomiting. Loss of consciousness rapidly follows and is associated with involuntary respiratory movements with aspiration of water. Convulsions may occur. Death comes after some minutes. These phases of drowning observed in animal studies have been extrapolated to human fatalities generally but are probably only applicable to individuals who suddenly find themselves submerged and unable to break the surface of the water. Many humans drown when there is no eyewitness evidence of any struggle.

Bodies Recovered from Water

The investigation of presumed drowning is a challenge because the mechanism of death in drowning is neither simple nor uniform, and the circumstances of drowning introduce more variables. Furthermore, not every body recovered from water is a victim of drowning. In practice, these deaths present as a generic problem of a body recovered from water and give rise to a set of generic questions to be answered by the investigation. These questions are as follows:

1. Did death occur before or after entry into the water (i.e., was the victim alive or dead at the time of entry into the water)?
2. Is the cause of death drowning? If not, what is the cause of death?
3. Why did the victim enter the water?
4. Why was the victim unable to survive in the water?

In order to resolve these issues, it is necessary to correlate information about the circumstances preceding the death, including the past medical history of the decedent, the circumstances of recovery of the body from the water, and the autopsy and associated laboratory analyses. Unfortunately, there are no autopsy findings which are pathognomonic of drowning. Therefore, obtaining proof that the victim was alive on entering the water and excluding natural, traumatic, and toxicological causes of death are critically important. Although some autopsy findings are characteristic of drowning, the diagnosis is largely one of exclusion and depends highly on the quality of the broader investigation.

All bodies recovered from water show a spectrum of postmortem artifacts resulting from immersion. These changes will occur in any corpse immersed in water, irrespective of the cause of death. The most common immersion artifact is maceration of the skin, which becomes blanched, swollen, and wrinkled, as a result of increased hydration of the epidermis. Maceration is first apparent in the skin of the fingerpads and then appears on the palms, backs of the fingers, and back of the hand, in that order. When fully developed, it is most striking on the palms and soles. In warm water, the early changes can be seen within an hour. Generally, obvious changes occur within 24–48 h, but the process may be delayed for several days in very cold water. With the development of putrefaction, the epidermis, including the nails, peels off like a glove or a stocking. Fingerprints may be easily prepared from the glove of epidermis. The remaining exposed dermis will yield a reverse fingerprint, which is technically much more difficult to obtain. Scars and tattoos are readily seen in the exposed dermis. Occasionally, chromogenic bacteria (*Bacillus prodigiosus* and *B. violaceum*) invade the dermis after a period of at least 1–2 weeks' immersion and produce patterns of pigmentation, giving the impression of tattoos. Cutis anserina, or goose-skin, is another common immersion artifact seen in freshly recovered bodies. This appearance is a roughening or pimpling of the skin as a result of rigor mortis of the erector pilae muscles associated with the fine hairs of the skin. It is most prominently seen on the thighs. It is of no diagnostic significance, and no importance should be attached to it.

A body in water will usually sink. Some bodies float because the specific gravity of a corpse is close to that of water and small variations, such as from air trapped in clothing, have a considerable effect on buoyancy. Having once sunk to the bottom, the body will remain there until putrefactive gas formation decreases the specific gravity of the body sufficiently to create the buoyancy that allows it to rise to the surface and float. Heavy clothing and weights attached to the body may delay but will not usually prevent the body from rising. The principal determinant of the rate of putrefaction is the temperature of the water, so that in deep, very cold water the body may never resurface because there is no appreciable putrefaction. In the water, a body normally floats face-down with the head, arms, and legs lower than the torso. Consequently, livor mortis (hypostasis) is most prominent in the head, neck, and anterior chest. Putrefactive changes, when they develop, are most prominent within these areas of lividity.

Having sunk to the bottom, a body drifting along the water bed or being washed ashore will sustain a pattern of postmortem injuries, reflecting its head-down floating position. Postmortem abrasions are typically found over the forehead, the prominent points of the face, the anterior trunk, the backs of the hands, and the fronts of the lower legs. A wide range of other injuries may be produced by the body battering against rocks or by passing watercraft in navigable waters. The body may be attacked by sharks, small fish, and other fauna. The soft parts of the face are particularly vulnerable to fish and crustaceans. Postmortem injuries may be inadvertently inflicted during the recovery of the body using grappling irons, hooks, and ropes. Postmortem injuries in areas of dependent lividity, such as the face, ooze blood, mimicking antemortem wounds.

Pathology of Drowning

Some autopsy findings are typical of drowning but are nonspecific and not universally present. None are pathognomonic of drowning. The concurrent observation of foam around the nose and mouth, frothy fluid in the airways, and emphysema aquosum with overlap of the medial edges of the two lungs is very strongly supportive of a diagnosis of drowning but may be found in only 10% or so of cases. The frequency of these observations decreases significantly with an increasing time of postmortem immersion, as a consequence of developing putrefaction. The fine white froth or foam may be seen exuding from the mouth and nostrils and is found in the trachea and main bronchi. Sometimes it is tinged with blood, imparting a pink color. The foam is a mixture of air, mucus, protein-rich pulmonary edema fluid, and, to a lesser extent, inhaled water, all whipped up by respiratory efforts. Thus, it is a vital phenomenon. However, it is not specific to drowning and is found in other instances of severe pulmonary edema, such as acute heroin overdose, congestive cardiac failure, and neurogenic pulmonary edema. In a body in water the foam persists until it is destroyed by putrefaction, which produces in turn pseudofoam of reddish-brown malodorous fluid containing bubbles of putrefactive gas, a finding of no diagnostic significance.

Emphysema aquosum (emphysème hydroaérique) is the second autopsy finding that is characteristic but not pathognomonic of drowning. Inhalation of the drowning medium, as well as reactive pulmonary edema and the struggling breaths of the victim, results in overinflation of the lungs and air trapping in the alveoli by fluid in the bronchial tree. The lungs appear ballooned, voluminous, and bulky. As a result, overlap of the medial edges of the two lungs is seen on removal of the breastplate at autopsy. The pleural surface of the lungs has a marbled appearance with gray-blue to dark-red areas that are interspersed with pink and yellow-gray zones of more aerated tissue. The lungs feel doughy and pit on pressure. On sectioning there is a flow of watery fluid. Although subpleural petechiae are rare, larger ecchymoses are sometimes seen, most often on the interlobar surfaces of the lower lobes. Subpleural bullae, which may be hemorrhagic, are occasionally found. These hemorrhages are a consequence of rupture of the alveolar walls, which is also the cause of blood tingeing of any foam in the airways. All of these findings in the lungs, although characteristic of drowning, may also be seen in cases of severe acute pulmonary edema from any cause. The microscopic appearance, reflecting the spectrum of macroscopic appearances, varies from being suggestive of drowning to entirely normal. Overdistension of the alveoli, thinning of the alveolar septa, and compression with narrowing of the capillary network are characteristic.

Contrary to expectations, lung weights in freshwater drowning are not statistically different from lung weights in saltwater drowning. The average combined weight of the two lungs in drowning in both media is approximately 1400 g with a standard deviation of approximately 400 g. These figures indicate that, in a minority of drowning deaths, perhaps amounting to 10–15%, the lungs are not heavy and waterlogged but rather are "dry." In the past, these cases were often characterized as "dry drowning," a confusing and misleading terminology that is not recommended. In the immediate postmortem period

following drowning, there is transudation of fluid from the lungs into the pleural cavity so that there is a time-dependent decrease in the lung weight and a reciprocal increase in the pleural effusion volume. Following saltwater drowning and continued immersion of the corpse for more than 3 days postmortem, there is a decrease in the combined lung and pleural effusion weights, likely the result of fluid shifts induced postmortem by the osmotic effect of the saltwater. Lung weights in drowning fatalities are significantly influenced by the gender and age of the victim, likely reflecting differences in individual physical constitution and survival times.

Material, such as sand, silt, seashells, and weeds, may be found in the airways, lungs, stomach, and duodenum of bodies recovered from water. Foreign material may enter the pharynx, trachea, and larger airways during submersion postmortem, and it is possible that small quantities may enter the esophagus and stomach. It is unlikely that foreign material will reach the terminal bronchioles and alveoli to any significant extent, if the postmortem submersion is short. Therefore, the finding of abundant foreign material generally distributed within the alveoli provides strong evidence of immersion during life, as long as the body is recovered early (i.e., within 24 h). Finding large quantities of sand in the upper airways raises the possibility of inhalation of the thick suspension of sand in sea water produced by heavy surf; death is very rapid in these circumstances. The presence of large quantities of water and contaminating debris within the stomach strongly suggests immersion during life. After submersion, the victim may attempt to breath-hold for as long as possible, and it has been shown that voluntary breath-holding can be extended by movements of the respiratory muscles and swallowing against a closed glottis. Thus, ingestion of large amounts of water is only likely to be found in those who attempted to extend voluntary breath-holding. The absence of the drowning medium in the stomach suggests either a rapid death by drowning, or a death from some other cause, such as a heart attack, while in the water, or death prior to entry into the water. Rarely, weeds, branches, and other material may be found fixed in the hand of the victim by cadaveric spasm (instantaneous rigor). This observation provides good evidence that the victim was alive and conscious at the time of submersion.

Victims struggling violently to survive in the water bruise or rupture muscles, particularly those of the shoulder girdle, neck, and chest. The hemorrhages tend to follow the lines of the muscle bundles and may be unilateral or bilateral. When external blunt-force trauma can be excluded, by the absence of skin injury or subcutaneous hemorrhage, then these muscle hemorrhages are strong indicators that the victim was alive in the water. They are found in a minority of drowning deaths, but the frequency of their observation is directly related to the care with which they are sought through dissection of the appropriate muscles. Uneven putrefaction can cause reddish patches to develop in muscles, and this may be confused with hemorrhage.

Middle-ear and mastoid air cell hemorrhages are occasionally seen in bodies recovered from water. These hemorrhages produce a blue-purple discoloration of the bone of the roof of the mastoid air cells and middle ear, which are visible after stripping off the dura mater following removal of the brain. Microscopically, there is congestion of the vessels and associated hemorrhage into the tissues of the external auditory canal, mucosal layers of the middle ear, including the eardrum, ossicles, and mastoid air cells. The pathogenesis is unresolved and may be the result of barotrauma, the irritant effects of aspiration of fluid into the eustachian tubes, or extreme congestion. Identical hemorrhages are found in cases of head trauma, electrocution, and mechanical asphyxiation, so that their presence does not constitute evidence of death by drowning.

The absence of a pathognomonic autopsy sign of drowning has led to a search for a diagnostic laboratory test. Awareness of the fluid and electrolyte shifts that may occur in drowning suggested measurement of the specific gravity of blood, plasma chloride, and plasma magnesium as possible diagnostic tests. However, these testing methods are no longer considered reliable because unpredictable changes in blood electrolytes always occur after death; postmortem fluid and electrolyte shifts occur between the drowning medium, the lungs, and the heart blood; and the relative role of fluid and electrolyte shifts in the mechanism of human drowning is unclear. Currently, the only diagnostic laboratory test for drowning to have gained widespread acceptance is the diatom test. Diatoms, or bacillariophyceae, are a class of microscopic unicellular algae of which approximately 15 000 species are known, approximately half living in fresh water and the other half in sea water or brackish water. The cell structure of diatoms is unique in that they secrete a hard silicaceous outer box-like skeleton called a frustule, which is chemically inert and almost indestructible, being resistant to strong acids. The classification of diatoms is based on the structure of their silicaceous valves. During drowning, smaller diatoms present in the drowning medium enter the systemic circulation, having passed through the filter of the lungs, and become lodged in tissues, such as the bone marrow, where they can be demonstrated

following acid digestion of the tissues. Lung tissue is not used for the tests since it can be readily contaminated postmortem by diatoms. The diatom test for drowning relies not only on the identification of diatoms in the bone marrow, but also the identification of the same species of diatoms as found in a sample of water obtained from the location of recovery of the body. Given adequate precautions to prevent contamination, the demonstration of diatoms of the appropriate species in organs, such as bone marrow, is strong corroborative evidence of death by drowning. This is true for decomposed bodies as well as fresh bodies, provided there is no gross mutilation of the corpse.

See Also

Autopsy: Procedures and Standards; **Injury, Recreational:** Water Sports

Sudden Infant Death Syndrome

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Introduction

There have been dramatic changes in the rates of sudden infant death syndrome (SIDS) since the 1990s due to public campaigns advising parents and child carers of risk factors such as sleeping face-down (prone), cigarette smoke exposure, and use of excessive bedding. At the same time developments in autopsy and death scene examinations and attempts to standardize procedures have resulted in improved accuracy of diagnosis in cases of unexpected infant deaths. This article deals with the approach to unexpected infant deaths and typical autopsy findings that may be found in cases of SIDS.

Definition

One of the major problems is that a number of definitions of SIDS have been applied with varying degrees of rigor over the years. This means that different research cohorts may have been defined quite differently from others and it may explain in part the great discrepancies that are sometimes found in the SIDS literature.

In 1991 the National Institute of Child Health and Human Development (NICHD) convened a meeting of experts who proposed that SIDS was "the sudden death of an infant under one year of age which remains unexplained after a thorough case investigation, including performance of a complete autopsy, examination of the death scene, and review of the clinical history." The significance of this definition was the emphasis on scene analysis and history review as integral parts of the investigation of possible cases. The definition is, however, one of exclusion and does not give weight to an association with sleep or to the findings of ancillary tests such as microbiological screening, skeletal survey, toxicological evaluation, and metabolic testing. Proposals have recently been made to stratify the definition so that cases with atypical features are more clearly identified.

Historical Background

SIDS has been documented as a cause of unexpected infant death for centuries: one of the first accounts is found in the judgment of Solomon in the Bible (1 Kings 3:16–28). Initially the cause of these infant deaths was thought to be accidental or deliberate suffocation of a sleeping infant by an adult who was sleeping or lying in the same bed. Wooden frames were devised to be placed over sleeping infants, and a mother or wet nurse who was found in bed with a dead infant without such a device could be excommunicated. Given the lack of autopsy examinations and formal investigations of these deaths in previous centuries it is not possible to have any accurate picture of death rates for specific conditions. Deaths due to sepsis and undernutrition were, however, common.

Developments occurred in the later part of the twentieth century whereby researchers started to look critically at possible causes of SIDS and interrelationships between endogenous and environmental factors.

Pathological Features

Unfortunately, there are no specific findings at autopsy that enable a conclusion of SIDS to be made based purely on the pathological features. Typically, an infant whose death is eventually attributed to SIDS shows no dysmorphic features, is well nourished, and has no significant underlying illnesses or injuries. However, the features of accidental or inflicted asphyxia may be identical in infancy to those routinely found at SIDS autopsies.

Features that are often present at autopsy include petechial hemorrhages of the thymus gland (**Figures 1** and **2**), epicardium and visceral pleura (**Figure 3**), blood-tinged oronasal secretions, pulmonary congestion, and edema. While nonpathologists often claim

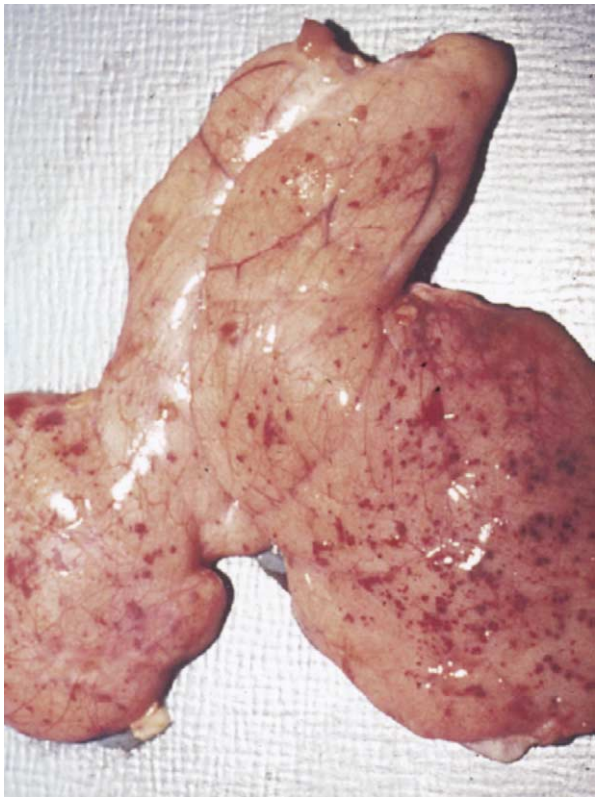

Figure 1 Scattered petechial hemorrhages of the thymus gland in a typical case of sudden infant death syndrome.

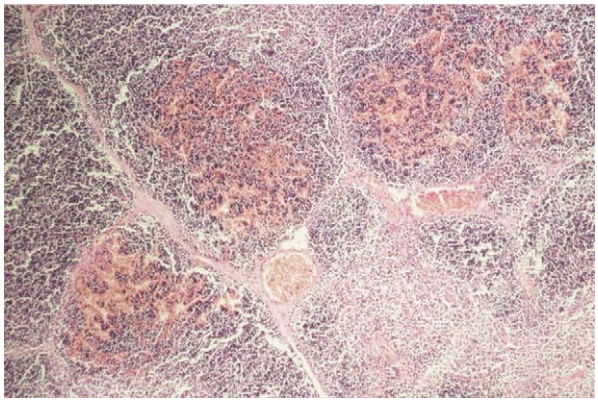

Figure 2 Interstitial hemorrhages within the thymus gland in a case of sudden infant death syndrome corresponding to petechiae noted macroscopically.

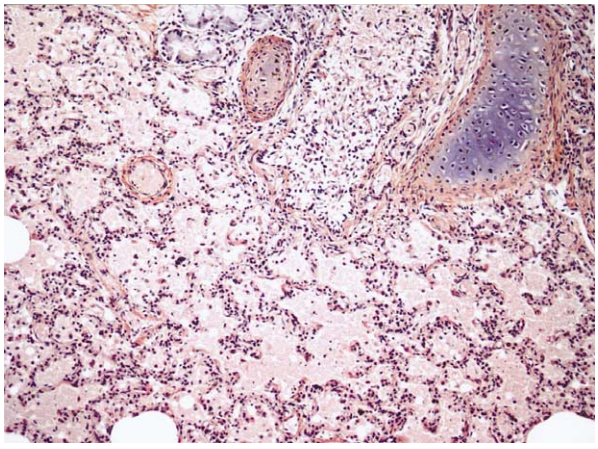

Figure 3 Photomicrograph of subpleural areas of lung demonstrating intraalveolar hemorrhage corresponding to petechiae noted macroscopically.

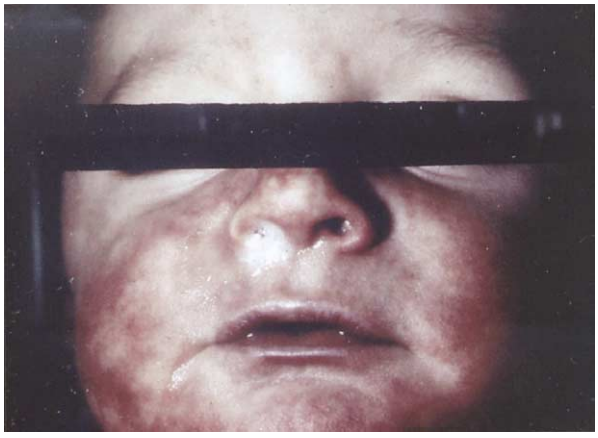

Figure 4 Foamy white pulmonary edema fluid in the nostril of a sudden infant death syndrome infant. Courtesy of WJ Klumann.

that the pathology findings are highly significant, experienced pathologists who perform autopsies on infants dying from an array of natural and unnatural conditions on a daily basis know that these findings are usually of minimal use in confirming or refuting different possible diagnoses.

Intrathoracic petechiae have been one of the most consistently described findings in infants who have died of SIDS, but are again in no way specific, as they are found in a variety of natural and unnatural deaths. They are demonstrated in 85–90% of SIDS cases and are most likely related to agonal gasping with increased negative intrathoracic pressure. The paucity of petechiae in the upper posterior portion of the thymus located in the neck above the innominate vein (Beckwith's sign) is in keeping with the effects of intrathoracic pressure changes, with protection of the cervical parts of the gland by the vein.

Oronasal secretions are usually present in SIDS infants and may fill the upper airway with frothy white pulmonary edema fluid (Figure 4), or may merely consist of a small amount of reddish fluid around the nostrils. The fluid derives from congested and edematous lungs and may be blood-tinged due to rupture of distal airway capillaries. Frank blood raises the possibility of an asphyxial event. Other

possibilities include damage to the upper airway from attempts at resuscitation or local nasal lesions such as vascular malformations, or areas of infection.

The lungs in SIDS infants are usually quite congested and edematous due to agonal left ventricular failure. Although it has been suggested that the finding of intraalveolar hemorrhage on microscopy indicates an asphyxial event, this finding is also nonspecific and has been shown to be influenced by the time between death and the autopsy examination, attempts at resuscitation, the position of the body after death, and sampling from dependent congested areas of the lungs. Similarly, hemosiderin within the distal airways may indicate previous asphyxial episodes, but it may also occur in SIDS infants who have no significant histories and otherwise unremarkable autopsies. Hemosiderin may also not be present in infants who have asphyxiated if there have been no previous episodes. Laryngeal basement membrane thickening is not a marker for SIDS infants.

Minor inflammatory infiltrates within lung sections are not an uncommon finding in SIDS cases. While it has been suggested that these areas of inflammation are a subtle indicator of a cause of death from the interaction of the infecting organisms, toxins, and cytokines, a recent study has shown no difference in the occurrence of such foci in SIDS and control infants who had died of trauma. These inflammatory foci are, therefore, present in a range of infants. While this does not rule out an idiosyncratic response to minor infection, any possibility of a relationship to the cause of death must undoubtedly account for a complex interplay of individual, and as yet ill-understood, susceptibilities.

Unexplained or significant trauma or significant occult organic diseases preclude use of the term SIDS. If myocarditis is found, with established myocyte necrosis, the cause of death is myocarditis and not the self-contradictory "SIDS with myocarditis."

When multiple infant deaths have occurred within the same family the cases require extensive investigation. The circumstances of the deaths and a detailed family history must be obtained and meticulously reviewed as the possibilities include homicide from inflicted suffocation or poisoning, or an inherited cardiovascular or metabolic disorder.

Autopsy findings in certain inherited cardiovascular disorders such as Romano–Ward or Jervell and Lange–Nielsen syndrome may be minimal and so cause confusion with SIDS. Infants with either of these syndromes have prolonged QT intervals on electrocardiography and may develop arrhythmias and sudden death. The diagnosis depends on the demonstration of specific mutations that involve *KVLQT1(KCNQ1)*, *HERG*, and *SCN5A* genes, and the *KVLQT1* and *minK (KCNE1)* loci on chromosomes 11p15.5 and 21q22 that are involved in potassium and sodium channels. If there is an underlying metabolic condition there may, however, be some autopsy evidence discernible. Cerebral edema with gyral flattening, and pallor of the liver, heart, and skeletal muscles may be present. Microscopically there may be storage material or fat within renal tubules, cardiac myocytes, or hepatocytes. The diagnosis usually requires intensive biochemical and molecular analyses.

Autopsy Approach

There has been an increasing awareness that the standard of autopsy examination in cases of unexpected infant deaths not only varies dramatically among countries but also within countries, and on occasion even between pathologists working within the same institution. The use of different definitions and dissection techniques with variable performance of ancillary testing has resulted in a confused picture emerging when cases have been reviewed. For this reason there have been strong moves internationally to standardize autopsy examinations for infants. Collaboration between researchers associated with SIDS International and the NICHD in the USA has led to the formulation of the International Standardized Autopsy Protocol (ISAP) (Table 1). This aimed at standardizing autopsy practices and improving diagnostic accuracy, providing additional information to supplement that obtained from the clinical history review and death scene examination, enhancing opportunities to reduce infant death rates, enabling more meaningful comparisons of infant death rates to be made between populations, and improving the quality of research into unexpected infant death. The ISAP has been endorsed by both the National Association of Medical Examiners (NAME) and the Society for Pediatric Pathology (SPP) in the USA. A number of other national autopsy protocols have also been developed in countries and regions such as the UK, Scandinavia, Germany, and Australia. Plans are developing for an update of the ISAP taking into consideration features that have been included or excluded from other protocols. A number of studies have validated the investigative steps that are specified in the ISAP and it has been clearly demonstrated that external examination, radiology, internal examination, histology, microbiology, toxicology, electrolyte and metabolic studies, and genetic studies have all contributed to significantly increased accuracy in diagnosis.

At around the time that the ISAP was produced there were also discussions about formalizing death

Table 1 International standardized autopsy protocol for sudden unexpected infant death

Decedent's name	*Local accession number*
Age/sex	Ethnicity
Date of birth	Date/time of death
Date/time of autopsy	Pathologist
County/district	Country

Final Anatomic Diagnoses

Microbiology results:
Toxicology results:
Chemistry results:
Pathologist_____

Decedent's name_____
Accession number_____
County and country_____
Pathologist_____

	Yes	No	
Microbiology Date/time:			
Done before autopsy			
Viruses: trachea, stool			
Bacteria: blood, CSF, fluids			
Fungi (discretionary)			
Mycobacteria (discretionary)			
Done during autopsy			
Bacteria: liver, lung, and myocardium			
Viruses: liver, lung, and myocardium			
Photographs, include:			
Name, case, number, county, country, date			
Measuring device color reference			
Consider front and back			
Gross abnormalities			
Radiographic studies, consider:			
Whole body			
Thorax and specific lesions			
External examination			
Date and time of autopsy			
Date and time of autopsy			
Sex (circle) male female			
Observed race (circle)			
White Black			
Asian Arab			
Pacific Islander Gypsy			
Hispanic, other (specify)			

Table 1 Continued

	Yes	No	
Rigor mortis: describe distribution			
Livor mortis: describe distribution and if fixed			
Weights and measures			
Body weight			g
Crown–heel length			cm
Crown–rump length			cm
Occipitofrontal circumference			cm
Chest circumference at nipples			cm
Abdominal circumference at umbilicus			cm

Decedent's name_____
Accession number_____
County and country_____
Pathologist_____

General appearance/ development	Yes	No	No exam
Development normal			
Nutritional status			
Normal			
Poor			
Obese			
Hydration			
Normal			
Dehydrated			
Edematous			
Pallor			
Head			
Configuration normal			
Scalp and hair normal			
Bone consistency normal			
Other			
Trauma evidence			
Bruises			
Lacerations			
Abrasions			
Burns			
Other			
Past surgical intervention			
Scars			
Other			
Resuscitation evidence			
Facial mask marks			
Lip abrasions			
Chest ecchymoses			
ECG monitor pads			
Defibrillator marks			
Venepunctures			
Other			

Continued

Table 1 Continued

General appearance/ development	Yes	No	No exam
Congenital anomalies			
External			
Integument			
Jaundice			
Petechiae			
Rashes			
Birthmarks			
Other abnormalities			
Eyes (remove when indicated and legal)			
Color: (circle) brown blue green hazel			
Cataracts			
Position abnormal			
Jaundice			
Conjunctiva abnormal			
Petechiae			
Other abnormalities			
Ears			
Low-set			
Rotation abnormal			
Other abnormalities			
Nose			
Discharge (describe if present)			
Configuration abnormal			
Septal deviation			
Right choanal atresia			
Left choanal atresia			
Other abnormalities			
Mouth			
Discharge (describe if present)			
Labial frenulum abnormal			
Teeth present			
Number of upper			
Number of lower			
Tongue			
Abnormally large			
Frenulum abnormal			
Other abnormalities			
Palate			
Cleft			
High arched			
Other abnormalities			
Mandible			
Micrognathia			
Other abnormalities			
Neck			
Abnormal			
Chest			
Abnormal			

Table 1 Continued

General appearance/ development	Yes	No	No exam
Abdomen			
Distended			
Umbilicus abnormal			
Hernias			
Other abnormal			
External genitalia abnormal			
Anus abnormal			
Extremities abnormal			
Internal examination			
Subcutis thickness 1 cm below umbilicus			
Subcutaneous emphysema			
Situs inversus			
Pleural cavities abnormal			
Fluid: describe if present			
Right, ml			
Left, ml			
Pericardial cavity abnormal			
Fluid, describe if present, ml			
Other abnormalities			
Peritoneal cavity abnormal			
Fluid, describe if present, ml			
Retroperitoneum abnormal			
Petechiae (indicate if dorsal and/ or ventral)			
Parietal pleura			
Right			
Left			
Visceral pleura			
Right			
Left			
Pericardium			
Epicardium			
Thymus			
Parietal peritoneum			
Visceral peritoneum			
Upper-airway obstruction			
Foreign body			
Mucus plug			
Other			
Neck: soft-tissue hemorrhage			
Hyoid bone abnormal			
Thymus			
Weight, g			
Atrophy			
Other abnormalities			
Epiglottis abnormal			
Larynx abnormal			
Narrowed lumen			
Trachea abnormal			

Continued

Table 1 Continued

General appearance/ development	Yes	No	No exam
Stenosis			
Obstructive exudates			
Aspirated gastric contents			
Endotracheal tube tip location			
Mainstem bronchi abnormal			
Edema fluid			
Mucus plugs			
Gastric contents			
Inflammation			
Lungs			
Weight			
Right			g
Left			g
Abnormal			
Congestion: describe location, severity			
Hemorrhage: describe location, severity			
Edema: describe location			
Severity (circle)			
Consolidation: describe location, severity			
Anomalies			
Pulmonary artery			
Thromboembolization			
Pleura abnormal			
Ribs abnormal			
Fractures			
with hemorrhages			
Callus formation			
Configuration abnormal			
Diaphragm abnormal			
Cardiovascular system			
Heart Weight			g
Left ventricular thickness			cm
Right ventricular thickness			cm
Septal thickness maximum			cm
Mitral valve circumference			cm
Aortic valve circumference			cm
Tricuspid valve circumference			cm
Pulmonary valve circumference			cm
Myocardium abnormal			
Ventricular inflow/outflow tracts narrow			
Valvular vegetations/thromboses			
Aortic coarctation			
Patent ductus arteriosus			
Chamber blood (circle) fluid clotted			
Congenital heart disease			

Table 1 Continued

General appearance/ development	Yes	No	No exam
Atrial septal defect			
Ventricular septal defect			
Abnormal pulmonary venous connection			
Other			
Location of vascular catheter tips			
Occlusive vascular thrombosis locations			
Other abnormalities			
Esophagus abnormal			
Stomach abnormal			
Describe contents and volume			
Small intestine abnormal			
Hemorrhage			
Volvulus			
Describe contents			
Colon abnormal			
Congestion			
Hemorrhage			
Describe contents			
Appendix abnormal			
Mesentery abnormal			
Liver abnormal			
Weight			g
Gallbladder abnormal			
Pancreas abnormal			
Spleen abnormal			
Weight			
Kidneys abnormal			
Weight			
Right			g
Left			g
Ureters abnormal			
Bladder abnormal			
Contents, volume			
Prostate abnormal			
Uterus, fallopian tubes, and ovaries abnormal			
Thyroid abnormal			
Adrenals abnormal			
Right			g
Left			g
Combined			g
Pituitary abnormal			
Congenital anomalies, internal			
Central nervous system			
Whole brain weight			
Fresh			g
Fixed			g

Continued

Table 1 Continued

General appearance/ development	Yes	No	No exam
Combined cerebellum/brainstem weight			
Fresh			g
Fixed			g
Evidence of trauma			
Scalp abnormal			
Galea abnormal			
Fractures			
Anterior fontanel abnormal			
Dimensions			
Calvarium abnormal			
Cranial sutures abnormal			
Closed (fused)			
Overriding			
Widened			
Base of skull abnormal			
Configuration abnormal			
Middle ears abnormal			
Foramen magnum abnormal			
Hemorrhage, estimate volumes (ml)			
Epidural			
Dural			
Subdural			
Subarachnoid			
Intracerebral			
Cerebellum			
Brainstem			
Spinal cord			
Intraventricular			
Other			
Dural lacerations			
Dural sinus thrombosis			
Brain: if externally abnormal,			
fix before cutting			
Configuration abnormal			
Hydrocephalus			
Gyral pattern abnormal			
Cerebral edema			
Herniation			
Uncal			
Tonsillar			
Tonsillar necrosis			
Leptomeningeal exudates (culture)			
Cerebral contusions			
Malformations			
Cranial nerves abnormal			
Circle of Willis/basilar arteries abnormal			

Table 1 Continued

General appearance/ development	Yes	No	No exam
Ventricular contours abnormal			
Cerebral infarction			
Contusional tears			
Other abnormalities			
Spinal cord			
Inflammation			
Contusion(s)			
Anomalies: other abnormalities			

Decedent's name_____
Accession number_____
County and country_____
Pathologist_____

	Yes	No
Mandatory sections taken		
Skin, if lesions		
Thymus		
Lymph node		
Epiglottis, vertical		
Larynx, supraglottlc, transverse		
Larynx, true cords, transverse		
Trachea and thyroid, transverse		
Trachea at carina, transverse		
Lungs, all lobes		
Diaphragm		
Heart, septum, and ventricles		
Esophagus, distal 3 cm		
Terminal ileum		
Rectum		
Liver		
Pancreas with duodenum		
Spleen		
Kidney with capsule		
Adrenal		
Rib with costochondral junction		
Submandibular gland		
Cervical spinal cord		
Rostral medullar junction		
Pons		
Midbrain		
Hippocampus		
Frontal lobe cerebellum choroid plexus		
Oil red O stained sections, if indicated		
Heart		
Liver		
Muscle		
Discretionary microscopic sections		
Supraglottic soft tissue		

Continued

Table 1 Continued

	Yes	No
Lung hilum		
Pancreatic tail		
Mesentery		
Stomach		
Colon		
Appendix		
Testes or ovaries		
Urinary bladder		
Psoas muscle		
Palatine tonsils		
Basal ganglia		
Metabolic disorders		
Retain on filter paper in all cases		
Whole blood (1 drop) urine (1 drop)		
Hair (taped down)		
Toxicology and electrolytes		
Fuid and tissues saved for 1 year		
Whole blood and serum, save at −70 °C and 4 °C		
Liver, save 100 g at −70 °C		
Frontal lobe, save at −70 °C		
Urine, save at −70 °C Bile		
Vitreous humor		
Serum		
Gastric contents		
Analyses performed, but not limited to:		
Cocaine and metabolites		
Morphine and metabolites		
Amphetamine and metabolites		
Volatiles (ethanol, acetone, etc.)		
Other indicated by history and exam		
Frozen tissues, save at −70°C		
Lung		
Heart		
Liver		
Lymph node		

CSF, cerebrospinal fluid; ECG, electrocardiogram.

scene evaluations. This led to the sudden unexplained infant death investigation report form (SUIDIRF) prepared by the US Centers for Disease Control and Prevention.

The establishment of gold-standard protocols has been done with the full recognition that not all of the recommendations will be able to be implemented in every jurisdiction due to variations in local conditions, cultures, and resources. For those reasons protocols are designed to act as templates for local adaptation. The aim is to provide a pathologist with as much information from the scene, medical and family history, and autopsy assessment of an infant as is possible before formulating a cause of death.

An example of local adaptation of international protocols is detailed below. This describes the approach to unexpected infant and early childhood deaths that has been adopted by the pediatric forensic pathology service at the Forensic Science Centre in Adelaide, Australia, and describes the type of interaction with other agencies that may take place to facilitate understanding of the circumstances of death. Particular specimens that are taken for testing, such as for toxicology, will vary depending on local laboratory practices and so will require close collaboration with toxicologists and microbiologists.

The Investigation of Unexpected Infant and Early Childhood Death in South Australia

An Overtly Suspicious Case

Following discussion of the case with attending police officers by telephone, the pathologist usually attends the scene, unless death has been in hospital. At the scene the pathologist liaises with police officers, who will include physical evidence section, major crime, criminal investigation bureau, family violence unit, and uniformed officers. The body is then examined and preliminary assessments are made as to the presence and nature of injuries, and the possible cause and time of death.

All Other Cases

The pathologist will liaise with police officers, examining the body at the scene, or in the mortuary at the earliest possible convenience. Discussion also occurs with attending officers regarding the possible transfer of bedding, medication, feeding bottles, and scene videos to the mortuary for examination before the autopsy is performed.

In All Cases

Details are obtained for:

1. the circumstances of death and events over the preceding 24 h
2. the presenting, and any hospital, histories (particularly regarding methods of attempted resuscitation)
3. prescribed medications, and any medications or drugs at the scene
4. details of sleeping arrangements
5. the infant or child's developmental level
6. any significant or recent illnesses
7. community health center records
8. any specific police concerns.

Contact is made with the following:

1. the local child protection officer/physician for possible further background hospital and community health center information. The child protection officer/physician may also be invited to attend the autopsy to assist in the evaluation of injuries
2. the local child abuse report line for further background information and notification of the case if there are concerns for the safety of other children in the family
3. the local Sudden Infant Death Syndrome Association for additional information if SIDS support workers have attended the family
4. ambulance officers if additional information is required from the scene
5. local medical officer/nursing staff if additional medical information is required
6. local children's hospital pathologists for case discussion with possible attendance at the autopsy
7. the state coroner.

External Examination

The body is examined for external evidence of trauma and neglect. Limb deformities, swellings, bruises, lacerations, burns, abrasions, skin, and conjunctival petechiae are documented. The external auditory canals and nasal septum are examined by otoscope. Rectal/anogenital trauma is documented, or excluded, and the core temperature is taken. The palms and soles of feet are examined for burns or injuries.

Radiology

A full skeletal survey is performed at the local pediatric hospital Department of Radiology before the autopsy. A verbal report is obtained from the reporting radiologist and radiographs accompany the body back to the forensic science center mortuary if injuries have been found. (X-rays are routine for children under 2 years of age and discretionary after this, depending on history, circumstances, and external examination.)

Photography

Full external photographs are taken in addition to photographs during the autopsy (of positive or negative findings). Photographs include the front and back of the body, close-ups of the face, conjunctivae (using eyelid retractors if necessary), the inside of the lips and mouth, the dissected neck, chest, abdomen, back and buttocks, and the pleural, peritoneal, and cranial cavities (with organs *in situ* and removed).

Autopsy Protocol

The autopsy examination of the three body cavities, soft tissues, and limbs is undertaken according to a modified ISAP.

Routine Specimens (see Table 2 for checklist)

1. peripheral blood from iliac vessels, if possible, for blood toxicology. This includes common prescription and illicit drugs, and alcohol (blood will usually have to be taken from the heart in infants)
2. urine, if available, for toxicology
3. sample of liver for toxicology
4. heart blood, after searing the right atrium with a heated spatula or washing with isopropyl alcohol, for: (a) blood culture (anaerobic and aerobic) (b) storage for DNA analysis if required.

Other specimens

1. cerebrospinal fluid for microbiology, by anterior lower spinal or posterior occipital approaches before removing the brain
2. lung and spleen swabs for microbiology
3. sample of heart for virology
4. blood spots on paper for metabolic screening
5. vitreous humor and liver for metabolic screening
6. liver, any spare blood (centrifuged for serum) and possibly gastric contents are stored in the freezer (liver and serum to be stored at –20 °C indefinitely)
7. hospital admission bloods and fluids are obtained by coronial warrant in suspicious cases for toxicological analyses.

Additional Steps to Usual Dissection and Organ Assessment

1. Measurements include crown–heel length, crown–rump length, head circumference, chest circumference, thickness of fat at anterior abdominal wall, and maximum width of anterior fontanels (normal values for age taken from standard charts are to be included in the autopsy report).
2. Skin and soft-tissue layer dissections of neck, anterior chest wall, abdomen, and back are performed. Buttocks (and possibly backs of legs) are incised for soft-tissue bruising (dissections are photographed).
3. Organs, in particular the heart with its venous and arterial connections, are examined *in situ* prior to evisceration of the body by the pathologist. The calvarium may be removed by the mortuary attendant but brain removal must be performed or supervised by the pathologist.
4. All organs are examined and weighed, including the thymus, adrenal glands, spleen, and pancreas (each lung and kidney is weighed separately)

Table 2 Checklist for cases of unexplained infant death

Case number:	**Date:**	
Attending personnel		
1. Police		[ ]
2. Physical evidence officers		[ ]
3. Child protection physician		[ ]
4. Pediatric pathologist		[ ]
5. Others (specify)		[ ]
Samples		
1. Blood/urine/liver for toxicology		[ ]
2. Blood/CSF for microbiological culture		[ ]
3. Lung/spleen swabs for microbiological culture		[ ]
4. Blood/vitreous/liver/skin for metabolic study		[ ]
5. Blood for DNA		[ ]
6. Heart tissue for virology		[ ]
7. Vitreous for electrolytes		[ ]
8. Liver/blood/gastric contents for storage (−70 °C)		[ ]
9. Filter paper storage	(a) blood spot	[ ]
	(b) urine spot (optional)	[ ]
	(c) hair (optional)	[ ]
Specimens		
1. Brain for neuropathology		[ ]
2. Cord for neuropathology		[ ]
3. Eyeballs		[ ]
Photographs		
1. Front, back, face		[ ]
2. Eyes, mouth		[ ]
3. Soft-tissue dissections		[ ]
4. Body cavities		[ ]
5. Other		[ ]
Phone numbers in cases of unexpected infant death		
Forensic technician		_____
Police communications		_____
Child protection pediatrician		_____
Child abuse report line/crisis care		_____
Pediatric pathologist		_____
SIDS association		_____
Ambulance officers		_____

CSF, cerebrospinal fluid; SIDS, sudden infant death syndrome.

(normal weights for age taken from standard charts are to be included in the autopsy report).

5. In all cases of unexplained or suspicious infant and early childhood deaths, the brain is sent to the local Department of Neuropathology for formal examination and staining of sections for amyloid precursor protein. The spinal cord is removed and examined. If no abnormalities are detected macroscopically, routine biopsies (×3) are taken. If there is any evidence of possible inflicted injury, or unusual features in the history or presentation, the spinal cord is also referred for neuropathological assessment. In such cases the eyeballs are also removed and sections stained for hemosiderin.
6. Samples taken for histology (in addition to any abnormal tissues) include the heart (×2 sections), lungs (×5), kidneys (×2), adrenal glands (×2), pituitary gland, thymus gland, submandibular gland, tonsil, thyroid gland (including adjacent trachea and esophagus), rib (marrow and bone growth plate), liver, stomach, esophagus, small intestine, large intestine, appendix, spleen, pancreas, mesenteric fat and lymph nodes, bladder, gonad, and uterus. Brain sections include frontal lobe, centrum semiovale next to the angle of the lateral ventricle, corpus callosum and parasagittal white matter, basal ganglia, hippocampus, occipital lobe, midbrain, pons, cerebellum and dentate nucleus, and medulla. A representative lung section is also stained for hemosiderin.
7. Samples taken for microbiological assessment (following searing of organ surfaces with a heated spatula, or washing with isopropyl alcohol) include a lung swab, spleen swab, blood culture from the right atrium, and heart tissue for virological study. The middle ears are examined and swabbed if moist or obviously infected.

Organ Retention

Retention of whole organs such as the brain, spinal cord, eyes, or heart for further specialist examination requires specific permission and formal authorization by the coroner.

Special Circumstances

1. Inflicted injuries are described as follows.
   - Bite marks are swabbed for DNA, photographed and examined by a forensic odontologist.
   - Finger or hand pressure marks are swabbed for DNA.
   - Cases of possible/definite sexual assault are examined in conjunction with the local child protection officer, following the taking of radiographs. Colposcopic videos may be taken. Semen and microbiological swabs/smears of the anogenital region, mouth, and pharynx are performed.
   - Representative fracture sites detected at autopsy, or shown radiographically, are removed for decalcification and histological assessment.
   - Bruises, burns, and skin lesions are sampled for microscopy (routine histology plus staining for hemosiderin).
   - Fingernail cuttings/swabs and head hair samples are taken for future DNA analysis if required.
2. Metabolic disease: the local pediatric hospital metabolic physician is contacted as soon as possible for case discussion and receiving samples. The autopsy may need to be performed immediately if a metabolic disorder is suspected.
   Specimens taken include:
   - an alcohol-swabbed, sterile skin specimen for fibroblast culture (taken fresh and not frozen)

- fresh samples of liver, skeletal muscle, heart, and brain for snap freezing
- urine
- blood
- vitreous humor.

All specimens require immediate transfer to a metabolic laboratory for processing or optimal storage.

3. Gastroenteritis/heat deaths/dehydration: Specimens to be taken include: (1) fecal swabs for microbiology; and (2) vitreous humor for electrolyte assessment.

Conclusions

The adoption of safe sleeping recommendations has led to substantially reduced numbers of SIDS deaths in many communities. Unfortunately, despite these successes, it has become clear that not all infant deaths have been investigated to an appropriate level in the past. This has resulted in the term SIDS being used too readily for suspicious deaths, or not at all when it should have been, when basic autopsy findings have been misinterpreted. Researchers have continued to publish results based on SIDS cases that do not fulfill the basic requirements of the NICHD definition, and unwarranted significance has been placed on nonspecific pathological findings to bolster unproven hypotheses.

Agreement on a common definition of SIDS and adoption of unambiguous and comprehensive autopsy protocols are required to reduce the chances of miscategorizing infant deaths. The range of possible diseases that may be found at autopsy in infants must be appreciated by pathologists who undertake pediatric cases, and their significance must be understood so that conditions can be correctly regarded as causative, contributory, or completely coincidental to death.

See Also

Autopsy: Pediatric; **Children:** Physical Abuse; Sudden Natural Infant and Childhood Death; **Imaging:** Radiology, Pediatric, Scintigraphy and Child Abuse; **Sudden Infant Death Syndrome, Etiology and Epidemiology**

Further Reading

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Autopsy, Findings, Adult Falls From Height *See* **Falls from Height, Physical Findings:** In Adults

Autopsy, Findings, Alcohol Use *See* **Alcohol:** Acute and Chronic Use, Postmortem Findings

Autopsy, Findings, Asphyxia *See* **Asphyxia**

Autopsy, Findings, Carbon Monoxide Poisoning *See* **Carbon Monoxide Poisoning:** Incidence and Findings at Postmortem

Autopsy, Findings, Pediatric Falls From Height *See* **Falls from Height, Physical Findings:** In Children