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CHAPTER 5

Forensic Toxicology in Death Investigation

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Forensic toxicology is a highly specialized area of forensic science which requires expertise in analytical chemistry, pharmacology, biochemistry, and forensic investigation. The practicing forensic toxicologist is concerned not only with the isolation and identification of drugs and other poisons from tissues, but also with the interpretation of his findings for the medical examiner, coroner, or other legal authority.

In our modern drug-oriented society the need for the services of a toxicologist is clear. The benefits received from medication are so well publicized that society tends to minimize the dangers and pitfalls. The American people spend over $9 billion a year on drugs. In 1971, the public spent approximately $5½ billion on prescription drugs and about $3½ billion for over-the-counter medications (Arena 1974). It has been estimated that there are as many deaths from drugs as from automobile accidents. During a 1-year period at the Montreal General Hospital, for example, 25 percent of the deaths on the public medical service were the result of adverse drug reactions (Martin 1971). Estimates of deaths from adverse drug reactions in the United States range from 3,000 to 140,000 (Talley and Laventurier 1974).

The cause of death in drug cases may range from a clear and obvious overdose, often substantiated by a suicide note, to a minor drug-related pathological process which, over an extended period, leads to a general decline in health. The latter situation is rarely recorded in mortality statistics.

THE MULTIDISCIPLINARY APPROACH TO DRUG DEATH INVESTIGATION

About 20 percent of all deaths occur in circumstances that, under the laws of most States, warrant an official investigation by the coroner or medical examiner to determine the cause of death. The resolution of many legal questions depends on the official pronouncement of the cause of death. The settlement of insurance claims often rests on the pronouncement of the death investigator. Accuracy in determining the cause of death depends on the cooperation and free flow of information among all members of the medicolegal investigative team: the police homicide investigator, the medical examiner's investigator, the forensic pathologist, the forensic toxicologist, and the medical examiner.

The homicide investigator is usually the first to view the scene and, if he is properly trained, it is he who maintains the scene undisturbed for the medical examiner whom he calls.

The medical examiner's investigator is frequently the only member of the medical examiner's staff to actually view the scene and talk to witnesses. He carries the main brunt of the investigation. He must obtain all information possible from the first officer on the scene, arrange for photographs of the body and the scene to be taken, collect and preserve all evidence including medications and empty containers found at the scene, interview all witnesses as well as family and friends, and obtain a medical history from family and/or attending physician. Several excellent references are available, in addition to chapters 2, 6, and 9 in the present book, to aid the investigator and the medical examiner: *Medicolegal Investigation of Death* (Spitz and Fisher 1973), *Homicide Investigation* (Snyder 1967), *Techniques of Crime Scene Investigation* (Svensson and Wendel 1972), and *The Pathology of Homicide* (Adelson 1974).

The forensic pathologist performs the gross autopsy, collects the proper specimens for analysis, and submits these specimens to the

toxicologist. Although gross findings in drug-induced and drug-related deaths are often nonspecific, e.g., visceral congestion and edema, discrete evidence suggesting poisoning by drugs has been documented (Svensson and Wendel 1972; Adelson 1974; Siegel, Helpern, and Ehrenreich 1966; Helpern and Rho 1966; Helpern 1972; Siegel 1972; Garriott and Sturner 1973; Citron et al. 1970; Hirsch 1972).

The forensic toxicologist is a crucial member of the team, and the objective laboratory evidence he gathers must be considered, evaluated, and explained in the final assessment of the cause of death.

COLLECTION AND PRESERVATION OF SPECIMENS FOR ANALYSIS

The evidence and information obtained by the toxicologist is only as good as the quality of his specimens. The proper specimens must not only be obtained uncontaminated, but must also be preserved in their original condition for the toxicological analyses to be meaningful. The human body is a dynamic organism even in death, and metabolism, oxidation, and bacterial growth may contaminate, modify, or destroy substances of interest so that they cannot be detected unless the specimens are properly preserved.

The pathologist should confer with the toxicologist concerning the choice and preservation of specimens, especially in cases requiring special treatment or exotic chemical analyses. Tissues other than blood should be promptly frozen upon collection. As for the blood sample, the toxicologist may prefer that it be collected in a chemically clean or a sterile container and maintained under refrigeration to avoid hemolysis. Chemical preservation may interfere with some toxicological assays.

It is recommended that samples of all tissues and fluids be obtained, placed in separate containers, and properly labeled at the time of autopsy regardless of the circumstances of the particular case. This procedure will help the toxicologist in his search for possible poisons throughout the body. It will also prevent disinterment of the cadaver, with concurrent toxicological problems caused by

the embalming fluid and decomposition if, due to new findings or history obtained following autopsy, a seemingly clear and straightforward case suddenly becomes suspect.

The specimen containers should be sealed with a coroner's or medical examiner's seal and appropriate arrangements made for delivery in order to maintain a valid chain of custody. A portion of each tissue must be saved by the toxicologist so that results of the analyses can be corroborated by another laboratory, should the occasion arise.

The size of the tissue sample required for the toxicologist to do his work will often be dependent on the instrumental capability of his laboratory. For example, if gas chromatography/mass spectrometry (GC/MS) with a computer data system is available, small quantities of each tissue may suffice. Conversely, if the laboratory is operating on a small budget with little instrumentation, very large samples may be desirable.

Fluids and Tissues Most Often Analyzed

The tissues to be collected may be dependent upon the drug or other toxic substance suspected. In any case involving the accidental or intentional overdose of drugs, blood, gastric contents, liver, bile, and urine (if available) should be considered minimal requirements for analysis. Regardless of how well the on-scene investigation is conducted, and the thoroughness of the autopsy, precisely what toxic compounds caused or contributed to death is sheer speculation until the chemical analyses are complete. Therefore, a large quantity of each tissue or fluid is always preferable. If a storage problem exists, temporary arrangements can usually be worked out with commercial cold-storage firms to meet security requirements for a minimal cost.

The choice of specimens and the quantity required do not pose a problem for the major medical examiners' offices in the United States since these operations are contained in a central facility and the pathologist and toxicologist are able to confer on each case. In a significant number of coroners' offices, autopsies are conducted in various hospital morgues and mortuaries and the tissues transported to laboratories some distance away. It

is often difficult if not impossible for the pathologist and toxicologist to confer on each case. Table 1 is offered as a guide for those pathologists to insure that adequate specimens are collected regardless of the nature of the case and the instrumental capability of the laboratory. As Adelson has pointed out (1974), when one is not sure what tissue to save, the only safe approach is to save everything.

Urine. Urine is a valuable fluid for the toxicologist since it enables him to perform simple screening procedures such as spot tests and immunochemical tests for drugs or drug classes, thus quickly informing him of their presence or absence in a certain concentration. Moreover, urine as the final depository of kidney drug excretion in many cases concentrates the drug and metabolites to levels that are readily detectable. Drugs and metabolites may still be present in urine when they are no longer detectable in the blood.

Blood. Blood is valuable as the circulating, bathing medium of the organs when uncontaminated by other body or tissue fluids. Purity and cleanliness of the blood specimen are essential for the correct interpretation of toxicological data. Contamination of the

specimen will render an already difficult task impossible or, worse, will lead to erroneous conclusions and interpretation. Two blood samples obtained from different body areas can serve as a check on each other and can provide evidence for uniform distribution of the drug in the blood. The forensic pathologist should be discouraged from using scooped-up or sponged-up "blood" from the body cavity after autopsy. The left side of the heart may be a better source of blood than the right because of possible diffusion of the drug from the liver to the right side. Peripheral blood is perhaps the best single sample.

Liver. The liver is the major site of biotransformation in the body and, as such, it concentrates many poisons and drugs. Poison may be detectable in the liver when none is detectable in the blood. The major part of the liver should be saved for toxicological analyses.

Although the human is dead, the liver's microsomal metabolizing enzyme system will be functioning and may well metabolize the drug or agent of interest before measurement is possible unless the chemical reactions are stopped or slowed. The process may be stopped or slowed by freezing the tissue immediately after autopsy and maintaining it in a frozen state until the assays can be performed.

Stomach and stomach contents. Often in overdose cases the intact tablets or capsules of drugs are found in the stomach at the time of autopsy and present a concentrated supply of the agent that can be readily identified. Even when no tablets or capsules are seen, their solubilized remains on the stomach walls may still present the best sample for identification. The total stomach contents, as well as the stomach, should be saved for analysis, and the toxicologist should report the total quantity of drug recovered.

Brain. Though the physiological action of many drugs lies in the brain, their concentration at this locus may not be very large. Nevertheless, many volatile poisons are retained by the lipid tissues of the brain and can most readily be assayed there. Brain cholinesterase should be assayed when organic pesticides are suspected (Curry 1969).

Vitreous humor. The vitreous humor may

TABLE 1. Suggested tissue collection in cases involving drugs
(See also table 1 in chapter 3)

Specimen[1]	Quantity
Blood	200 ml
Liver	500 gm
Brain	200 gm
Kidney	equivalent of one
Bile	all available
Lung	500 gm
Adipose tissue	50 gm
Gastric contents	all available
Urine	all available

[1]In certain cases, other specimens such as vitreous humor, hair, nails, etc., may be indicated.

prove useful for various clinical chemistry determinations (Siegel 1972; Garriott and Sturner 1973; Citron et al. 1970; Hirsch 1972; Curry 1969; Coe 1969; Coe and Sherman 1970; Sturner and Coumbis 1966; Coe 1974) and may well be the specimen of choice for alcohol in certain instances (Sturner and Coumbis 1966; Coe 1974). Coe and Sherman (1970) have found that chemical changes for many substances occur more slowly in vitreous humor than in blood. For certain determinations, hemolyzed blood is unacceptable. Garriott (1974) has been able to determine digoxin values more accurately using vitreous humor rather than blood collected postmortem in coroner's cases.

Kidney. Johnston, Goldbaum, and Whelton (1969) have found that morphine concentrations of 0.2 mg/100 gm or more were present in the kidneys in cases of sudden death caused by the intravenous use of heroin. They suggest that drug levels in kidney tissue may be a good indicator of death that occurred rapidly following heroin injection. The kidney is also considered a tissue of choice in cases involving heavy metals and sulfonamides.

Lung. The lung is a tissue of choice in cases involving inhalation of a drug. High concentrations of many drugs taken intravenously (for example, morphine) or orally (for example, propoxyphene) may also be present.

Bile. A number of important drugs, for example, glutethimide and morphine, are eliminated through biliary excretion. In cases of prolonged survival time following heroin injection, the bile may be the only specimen other than urine which can provide the analyst with a sufficient concentration of morphine for detection.

Adipose tissue. Certain chemical compounds will accumulate in the fat and, in those cases in which the victim has survived for some days following ingestion, this tissue may offer the only proof of the compound ingested. Glutethimide (Goldbaum, Williams, and Johnston 1962), ethchlorvynol (Cravey and Baselt 1968) and thiopental (Goodman and Gilman 1971) are among the drugs which are accumulated in adipose tissue. If a sample of fat has not been collected by the pathologist, the peripheral fat from the kidney can be analyzed.

METHODOLOGICAL APPROACH TO IDENTIFICATION OF DRUGS

The onsite investigation and the autopsy findings often provide the analyst with clues to the possible offending agent. At the onsite investigation, any evidence of drugs, pesticides, or other harmful agents should be collected and preserved. A thorough questioning of the victim's social contacts can many times provide useful leads for the toxicological analysis. The astute investigator may save the toxicologist many hours or days of effort. Reports of the onsite investigation and the autopsy findings should, therefore, be made available to the toxicologist so that he may use pertinent information to minimize his analyses. When no evidence is found at the scene, and the autopsy shows no clear findings, a number of toxic substances must be searched for routinely, and the toxicologist is then presented with a general unknown. It is the belief of many toxicologists that, if an adequate history were obtained and a complete onsite investigation and a thorough autopsy were performed and followed by microscopic studies, the occurrence of general-unknown cases would be greatly minimized. The routine poison screen devised for general use will change from locality to locality depending, for instance, on the local drug subculture and whether an agricultural or urban community is served.

Separation of Drugs and Their Metabolites From Tissue

Although some tests may be performed directly on specimens such as urine or gastric lavage, the majority are performed on organic solvent extracts of body fluids or homogenized tissues. Many methods exist for the isolation of drugs and their metabolites from blood and other tissues. Niyogi (1970) has published a comprehensive critical review of many of these methods. Ultimately, the selection of an appropriate means of extraction for screening purposes will depend on exactly which drugs, or groups of drugs, the toxicologist wishes to isolate. Most forensic toxicologists will extract the specimen into organic solvents at different pH's, thus separating into strong acids, weak

acids, bases, and amphoteric drug fractions. Excellent references to this systematic approach are found in Stewart and Stolman (1960, 1961), Sunshine (1969, 1971), Stolman (1963, 1965, 1967, 1969), Kaye (1970), Curry (1969, 1972) and Clarke (1969).

Other means of separating drugs and their metabolites from tissues or fluids include distillation, digestion, and chromatographic methods. In recent years, amberlite XAD-2 polymeric adsorbent resin extractions have been widely used. This involves a one-step application at pH 8.5 to isolate acidic, neutral, basic, and amphoteric drugs, though at less efficiency than the usual organic solvent extraction. Recovery can be improved for particular classes of drugs by altering the pH at which the fluid is applied to the XAD-2 column. A pH of 8.5 is often recommended because it is optimal for morphine, thus capable of identifying cases from methadone maintenance programs. Urine is applied to the wet column after being adjusted to pH 8.5 and allowed to filter through the resin. The drugs are then eluted from their binding sites on the resin with ethylene dichloride, which is then treated as the organic layer of a classical extraction procedure.

METHODS OF ANALYSIS

Chromatographic techniques are most often used in the forensic laboratory for both qualitative and quantitative tests for drugs and metabolites. Among these techniques are column, paper, high pressure liquid, thin-layer and gas-liquid chromatography. Descriptions of the latter two follow:

Thin-layer chromatography (TLC) provides a simple, reasonably inexpensive, and sensitive method of analysis. Drugs are separated on the basis of their molecular structure and properties and may be identified using parameters such as Rf[1] value and reaction to a series of chromogenic reagents. Positive results should not be based on one solvent system alone; several systems, each yielding different Rf values for the drugs of interest, should be used. TLC methods are empirical, qualitative, and somewhat nonspecific. Many man-hours of practice are necessary to acquire confidence and expertise. In general, TLC is useful as a screening tool. It is advisable to use other independent analytical methods in the forensic laboratory before definitive identification is concluded. Forensic scientists appear to be in agreement that a minimum of two different parameters must be utilized for positive identification.

Gas-liquid chromatography (GLC). Among the analytical tools available to the toxicologist, no single tool, probably, proves more useful than the gas chromatograph. It can provide a rapid, versatile, sensitive, and specific means for separating, identifying, and quantitating components of a complex mixture. It can offer a unique method for isolating a compound in question in pure form for identification by other means. Gas chromatographic columns of many different polarities and properties are readily available from commercial sources or can be made in the laboratory to accomplish almost any separation. A refinement of the GLC technique is the formation of derivatives of the drug before injection into the gas chromatograph. Derivative formation, an important identification technique in classical organic chemistry, in combination with gas chromatography is a powerful tool in the toxicologist's repertoire. Moreover, some drugs may not optimally separate on GLC unless derivatives are made.

Absorption Spectrophotometry. Absorption spectrophotometry is a most useful routine tool in a toxicology laboratory. A vast amount of spectral data (visible, ultraviolet, and infrared) has been collected over the past 25 years and provides a rich data bank to be used by the toxicologist. Infrared spectrophotometry provides more information than either visible or ultraviolet, inasmuch as every chemical compound produces its own characteristic spectrum, not unlike a fingerprint. However, purification of the unknown compound prior to its introduction into the infrared spectrophotometer is essential.

Ultraviolet and visible spectrophotometry have a greater practical application in the forensic laboratory than has infrared, in that

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[1]Rf = $\dfrac{\text{distance traveled by substance from starting point}}{\text{distance traveled by solvent from starting point}}$

valuable information can be obtained often with little or no purification, and it provides a quantitative measurement for many drugs when they are present at toxic levels.

Mass Spectrometry (MS). Mass spectrometry has recently become a powerful tool in the toxicology laboratory since it provides molecular weight and fragmentation pattern information and is, therefore, a highly selective method. The integrated coupling of the gas chromatograph with the mass spectrometer allows the use of the strongest features of both techniques. GC/MS computer systems appear to offer the best instrumental technique now available for the positive identification of drugs and metabolites because, while it is possible for compounds to have the same mass, no two compounds are likely to have the same intensity and distribution of fragmentation peaks. Reference mass spectral data have been accumulated by a number of spectroscopists and can be conveniently used in a computer library search for the identification of drugs and metabolites or in a manual search (Finkle, Foltz, and Taylor 1974).

Immunochemical Techniques. Excellent reviews, discussions, or descriptions of immunochemical techniques are available (Sunshine et al. 1974; Bidanset 1974). In a search for more sensitive screening methodologies, the toxicologist has currently turned to immunochemical techniques including hemagglutination-inhibition, radioimmunoassays (RIA) and enzyme-multiplied-immuno-techniques (EMIT). All the immunochemical methodologies take advantage of the sensitivity of the antigen-antibody reaction. The drug in question is covalently attached to a protein, the complex then injected into an animal, thus stimulating production of antibodies to the drug-protein antigen. The antibodies to the drug hapten are then isolated and used in the immunochemical assays. The primary reaction in all the various immunochemical systems is the antibody-drug hapten reaction. The difference in the various methods arises in the monitoring of this reaction. In hemagglutination-inhibition, the inhibition of agglutination of red cells coated with the drug is the indicator reaction. In RIA, a small sample of radioactive drug is mixed with the unknown sample and, using a constant amount of antibody, the amount of radio-

activity bound to the antibody is measured. The amount of drug in the unknown sample is read from a standard curve.

EMIT assays use enzyme labels in place of radioactive labels. In this test an antibody is prepared which is specific to the drug to be assayed. An enzyme, lysozyme, is attached to the drug of interest so that the enzyme cannot act on its substrate when it is bound by the antibody. When the unknown serum or urine sample to be analyzed is mixed with the antibody and enzyme-labeled drug, any free drug molecules in the specimen will compete with the enzyme-labeled drug molecules for the limited number of antibody binding sites. The enzyme activity is then measured by adding the substrate for the enzyme to the mixture. The free unbound lysozyme acts on the substrate bacterial cells causing them to lyse and the solution to change in optical density at a rate proportional to the concentration of free enzyme in the mixture. The reaction can be measured in an inexpensive spectrophotometer.

The critical essence of immunochemical assay methods is the rarity of false negatives. If the drug is there, it will be so indicated, but there can be and there are many false positives arising from drug metabolism, from other members of the same class of drugs, and from cross-reactivity of the antibody preparation. The antibody was manufactured to "see" parts of the hapten, and thus all molecules having these parts will be "seen" as the drug.

A great advantage of immunochemical techniques is that they may be performed on body fluids without prior time-consuming, sensitivity-lowering organic extractions. This characteristic, in conjunction with their great sensitivity and the lack of false negatives, makes the immunochemical methods well suited for screening.

On the negative side, it should be pointed out that confirmation in coroner's cases is essential and often there is difficulty in substantiating positives using other, less sensitive techniques.

The only truly specific techniques available to the toxicologist are mass spectrometry and infrared spectrophotometry, which relate to molecular structure. The former may be prohibitive due to cost, and the latter may prove inadequate due to required sample size.

Finkle (1972) has stated that, where a single specific identification technique is not available, cumulative analytical data are acceptable for identification.

Quality Control

The crucial point that must be kept in mind in utilizing any method is the concurrent analysis of properly prepared standards alongside the unknowns. The importance of this point cannot be overemphasized. These standards should, as closely as is feasible, approximate the composition and drug concentrations of the specimens. Because the concentration of the drug in the sample to be analyzed is unknown, a series of standards of various concentrations prepared in the same body fluid as the unknowns is the best practical policy to follow. By doing this, one can check the linearity of the assay method and control for nonlinear response at high or low drug concentration, as well as having a standard at a concentration similar to that of the unknowns. The comparison aspect, standard vs. unknown, of these methods allows automatic correction for different drug concentrations, dependent or independent recoveries, different analyst manipulations, differences in sensitivity of instrumentation, and many other variables that would otherwise render the assays inadequate, inaccurate, or imprecise.

Another important reason for running a set of standards is for quality control purposes. A toxicologist must always suspect his results unless clear and abundant evidence are presented to show that the method, the operator, and the instruments were all operating within the limits of acceptable error. For these reasons, one must conduct a strong in-house quality control program assisted by a regular outside proficiency testing service. The need for a regular outside proficiency testing service has been demonstrated and reported by Dinovo and Gottschalk (1976).

Barnett (1974) considers two practical types of quality control: internal, which makes use of stable material to be included each day or in each batch; and external, in which samples from outside sources are introduced periodically for blind analysis. The latter may be in the form of proficiency surveys. He notes that quality control is a good tool for

quantifying how poor our analytical methods are. It contributes nothing toward improving these methods or our use of them, but it does help us isolate poor methods so that better ones may be substituted.

THE INTERPRETATION OF TOXICOLOGICAL FINDINGS

One of the most difficult problems the forensic toxicologist encounters is that of interpreting his analytical findings. A table of "therapeutic" blood concentrations would be of great value, but unfortunately this information is limited in the literature and, where it is available, usually these studies have been limited to very few subjects representing only a young healthy population. The tabulation of toxic and therapeutic drug concentrations of Baselt, Wright, and Cravey (1975) is shown in appendix D. More recently Winek (1976) and Dinovo et al. (1976) have published similar tables of therapeutic and toxic drug concentrations. Tissue concentrations from fatal cases are more readily available and can be found primarily in the journals devoted to the forensic sciences and the books on toxicology (see also chapter 4 of this book). In recent years, the *Bulletin of the International Association of Forensic Toxicologists* has been an excellent source of information on methods as well as fatal tissue concentrations. Information from well-documented and well-investigated cases that the toxicologist personally obtains greatly enhances his ability to interpret values.

However, in drug-induced and drug-related deaths, other factors must be taken into consideration in addition to concentrations of drugs: among these are age, pathology, route of administration, tolerance, and the interaction of drugs in combination.

Age. It has long been recognized that the young may be more sensitive to drugs than are adults. Moreover, according to Goldstein, Aronow, and Kalman (1974), infants are likely to show more prolonged effects to some drugs. Fingl and Woodbury (1965) state that children are often hypersensitive to certain drugs, especially those that produce central nervous system stimulation or depression. Deichman and Gerarde (1964) state that after

the absorption of a toxic dose of ethanol, children fall asleep rapidly and remain unconscious for a significantly longer period than do adults. The physiological effect of some drugs may be different on children than on adults; for instance, amphetamines tend· to calm hyperactive chilaren, while they excite and stimulate adults.

Roberts (1974) suggests that, at the other end of the age spectrum, the response of the aging heart to drugs deserves more study. His experiments have involved quinidine and digitalis in the elderly. He notes, for example, that quinidine may be less effective in the treatment of older patients, and that older patients seem to be more likely to suffer from "digitalis arrhythmia."

Pathological states. Serious pathological changes in organs and systems must be considered in postmortem tissue concentration of drugs. For example, Petty (1967) uses the weight of the heart, disease present, and liver pathology in judging ethanol fatalities. He has found blood alcohol concentrations as low as 50 mg/100 ml in deaths due to acute alcoholism where serious pathology existed in the heart and/or liver.

Goldstein, Aronow, and Kalman (1974) note that drugs are likely to have enhanced or prolonged effects in patients with liver abnormalities. This may be due to decreases of the microsomal drug-metabolizing system. The inability to metabolize drugs in the diseased liver would produce excessive or prolonged response to ordinary doses of drugs. If the drug taken is converted to an active metabolite, a decreased response would occur in a diseased liver unable to effect metabolism. Impaired renal function is another consideration since multiple dosage may build up to toxic concentrations if the elimination rate is substantially diminished.

Route of administration. Possible routes of entry are external (sublingual, oral, or rectal) and parenteral (subcutaneous, intravenous, intramuscular, intradermal, inhalation, or skin application). In the majority of coroner's cases, administration is oral or intravenous. Toxic effects may occur from intravenous administration that would not be expected if the same dosage were given orally. Too rapid an injection rate may cause the blood pressure to fall with ensuing circulatory and respiratory

irregularities. This untoward effect is sometimes referred to as "drug shock" and, due to the speed of onset, resembles anaphylactic shock. Acute allergic responses may also occur and undoubtedly other mechanisms of action exist which are not well understood.

In some cases, the concentration of drug in the blood at the time of death is low, if given intravenously, as compared to fatal blood concentrations following oral ingestion.

Drugs in combination. The interaction of drugs in combination must be evaluated in considering the case. The effect may be additive, antagonistic, or synergistic. The first terms are self-explanatory. *Synergistic* refers to the combined effect of drugs in combination being greater than the sum of each acting independently. The combination of alcohol with narcotics or barbiturates may be lethal at comparatively low doses of drugs. Recently Dinovo et al. (1976) have reported on the toxicological examination performed on 2,000 drug-involved deaths. They found that alcohol potentiates the effect of barbiturates as well as of imipramine, amitriptyline, meprobamate, thioridazine, morphine, propoxyphene, and methaqualone. The concentration of alcohol alone or drug alone may not be at the "fatal" level, but the astute toxicologist will be aware of possible synergistic effects and will, therefore, suspect lethal drug effects.

Tolerance. Tolerance, a state of decreased responsiveness to a drug, may occur upon prolonged use of drugs. Therefore, a knowledge of the decedent's history of drug use is of the utmost importance in evaluating the tissue concentrations found by the toxicologist.

Let us consider the example of tolerance to amphetamine. Peak plasma concentrations in human subjects following the administration of 10-15 mg of amphetamine sulfate range from 0.001 mg/100 ml to 0.005 mg/100 ml, according to Campbell (1969). Driscoll et al. (1971) reported a blood concentration of 0.002 mg/100 ml 2½ hours following the ingestion of 12.5 mg of methamphetamine. As cited earlier, fatal cases have been attributed to blood levels less than 0.1 mg/100 ml. Cravey and Jain (1973) analyzed multiple blood specimens taken at various times of the day from a tolerant user of amphetamine who required approximately 1 gm daily. In order

to feel "normal" she needed to maintain a blood concentration ranging from 0.2-0.3 mg/ 100 ml. During this maintenance period, in which she was observed on medication prior to detoxification, she was calm and slept well without sedation. Her pulse rate was not increased, and her temperature was not elevated. (See also the discussion of tolerance in chapter 4.)

Other factors. Additionally, sex, genetic and dietary differences, and variability in drug responses in individuals, among other factors, may be important in interpretation of fatal cases. The recommended dose of a drug should produce the desired effect in the majority of a population, but in a small percentage will produce no measurable pharmacologic effect and in a still smaller percentage may produce a mild to moderate toxic effect.

WHAT SERVICE CAN THE FORENSIC TOXICOLOGIST PROVIDE THE MEDICAL EXAMINER?

Since it is the legal obligation of the medical examiner to certify that the cause and mode of death conform with medical and scientific facts in all cases of sudden and unexplained death, complete toxicological analyses are essential to complete investigation. In drug-induced and drug-related deaths, some evidence of the foreign chemical or its specific toxic effect must be found in the body of the deceased, or no positive proof exists of their role in the terminal episode.

The tissue concentrations, together with an estimate of the total amount of drug remaining in the stomach at the time of death, not only offer information regarding the degree of toxicity expected but often prove helpful to the medical examiner in his determination of intent, i.e., accidental vs. suicidal.

The toxicologist should be encouraged to perform "body distribution studies," particularly in those cases involving newer drugs and toxins about which little is known. The medical examiner and the toxicologist are in a unique position to study distribution and metabolism of drugs in human cases in which the compounds have been ingested in meaningful quantities. Such cases cannot be replicated by the scientific community, and much valuable information is irrevocably lost when such cases are not thoroughly studied.

It is through these complete toxicological studies that the forensic toxicologist gains expertise in the interpretation of tissue concentrations so vital to the medical examiner. The recent advent of instrumentation capable of measuring sub-nanogram concentrations, together with body distribution studies and careful investigation by other members of the medical examiner's team, have enhanced our knowledge regarding previous problem areas. For example, up to about a decade ago, urine and bile were regarded as specimens of choice in the laboratory investigation of deaths due to intravenous narcotism. Consequently, the laboratory offered no proof to the medical examiner in numerous cases, since those specimens often did not show a detectable concentration of morphine. Body distribution studies, together with case histories, have changed this concept. In those cases where death ensues rapidly following intravenous administration, high concentrations of morphine will be found in the blood, brain, and lung. And often we find that, if the victim has been drug-free prior to injection, no detectable concentration is found in the bile and urine. As previously cited, Johnston, Goldbaum, and Whelton (1969) through distribution studies concluded that a kidney concentration of morphine above 0.2 mg/100 ml is an index to short survival time. And Garriott and Sturner (1973) recently correlated blood morphine concentrations and distinct pathology with survival time.

Finding alcohol and other drugs which may have led to decreased mental functioning, or may have produced various psychic disturbances, can help to explain a variety of traumatic deaths such as automobile accidents, industrial accidents, drowning, and sometimes homicides. In addition to the forensic toxicologist's aid in explaining suicides and accidental deaths, his negative or therapeutic concentration findings will be equally important to the medical examiner.
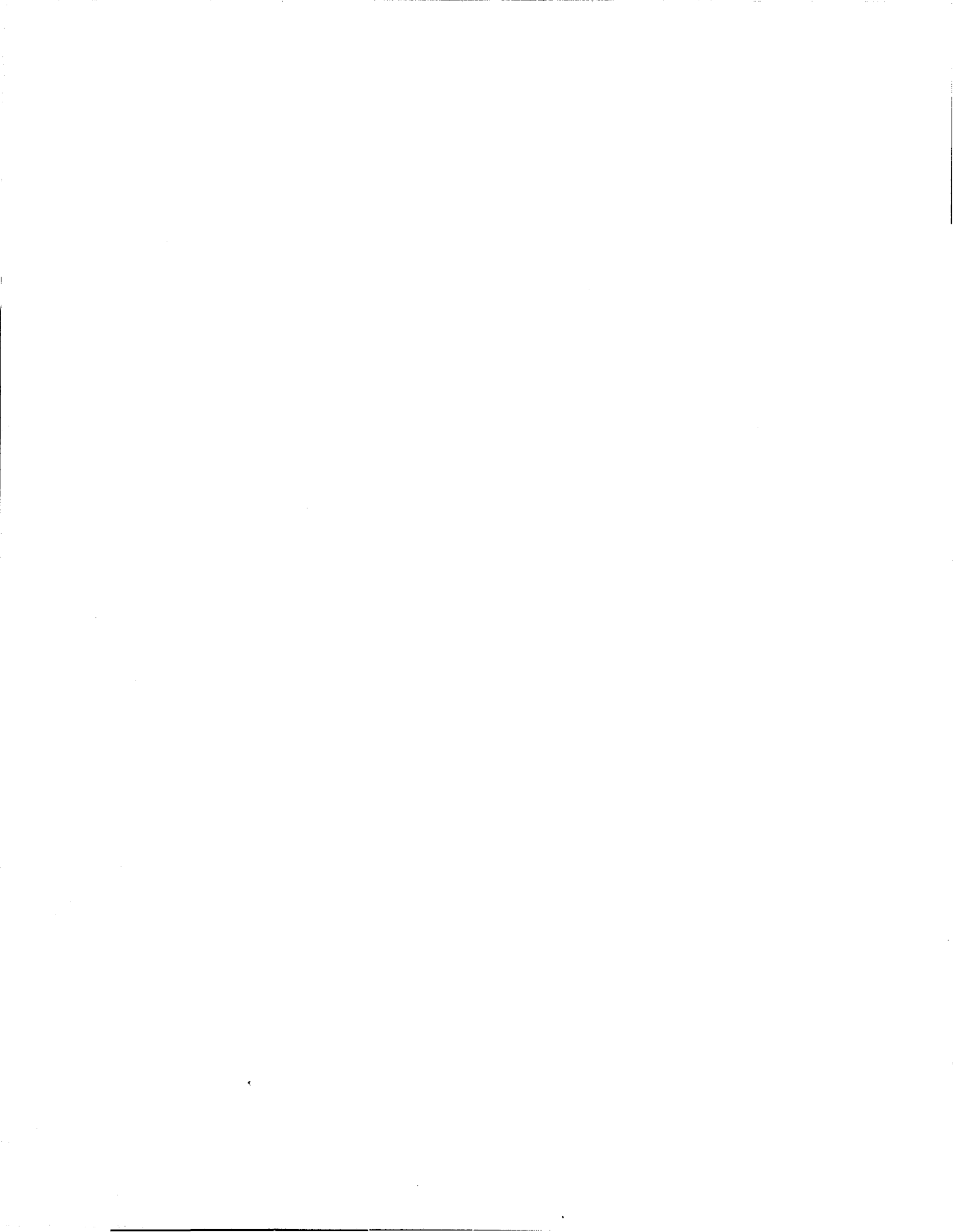
In conclusion, the prevalence of drug-induced and drug-related deaths is quite significant and rising in our drug-oriented society. The forensic toxicologist can aid the coroner or medical examiner in his search for the cause and manner of death by his knowl-

edge and expertise in a difficult scientific specialty and by his technical capacity to find evidence showing the role that the ubiquitous drugs of our society play in unexplained deaths.

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