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ANALYSIS OF DRUGS OF ABUSE

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FOREWORD

The object of this series of monographs is the timely dissemination of essential information about topics of current interest in science. Interdisciplinary aspects are given fullest attention. The series aims at the presentation of new techniques, ideas and applications in sufficient detail to enable those who are not specialists in a particular subject to appreciate the applicability of the subject matter to their own work, and the bibliographies included in each monograph will guide readers in extending their knowledge of the subject to any desired depth. The depth of treatment of course makes them compact definitive books for the specialist as well. The series will from time to time include more general reviews of selected areas of scientific advancement, for which a somewhat wider readership is envisaged.

The series is to be priced at a level to attract the individual purchaser as much as the librarian. The topics and the depth of treatment should suit both the student and the research worker, academic or industrial. The range of topics in this series will eventually span the whole extent of scientific interests and the authorship will reflect the international nature of the subject matter.

Analysis of Drugs of Abuse is not a cook-book of analytical recipes. In keeping with the aims of this series of monographs it presents a critical review of the analytical methods used in toxicological investigations, details the application of these methods to the analysis of various families of drugs, and illustrates the advantages and pit-falls by reference to a number of actual cases drawn from the author's considerable experience of toxicological investigations. Throughout the book the author stresses the importance of clinical factors in reaching a decision as to whether a particular drug has been used and in assessing the physiological significance of the amount found. This book will be of interest to all those actively engaged in drug analysis and also to all readers interested in the drug-abuse problem and in the analytical methods available for its control.

L. C. Thomas

PREFACE

That meeting of the Royal Society, London in 1885 at which W. N. Hartley discussed his investigations concerning ultraviolet absorption spectra of principal alkaloids can be considered a milestone in the development of present day techniques of analysis. Although his instrumentation was relatively crude by current standards, he was able to demonstrate that substances like quinine, morphine and cinchonine yield highly characteristic ultraviolet absorption spectra which can be used for both identifying them and ascertaining their purity. Hartley also showed that alkaloids closely related in structure, e.g. morphine and codeine, have very similar spectra.

Perhaps it should not be too surprising that this early instrumental application to drug identification, so impressive to us, was greeted with less than enthusiasm by certain colleagues present. One austere gentleman stated, rather angrily, that he foresaw the day when 'the expert' would be supplanted by ignorant girls with machines.

That learned gentleman has been proven a Cassandra in part only. While many who would perform these drug analyses tend to function primarily as 'glorified button pushers' or tyro cooks following recipes blindly, the true practitioner of the art/science of toxicology strives to be an analyst who not only understands the basic chemistry involved in the analysis of the substances concerned (drugs, toxic metals, etc.), but is also cognizant of the principles, capabilities and limitations of instrumentation applied in such analyses. How absolute is the identification of the substance in question?

In order to function efficiently, in a meaningful manner, the analyst must, in addition, be knowledgeable concerning effects exerted on a living organism by the substances under scrutiny. Of what significance is the quantity or level found? Does the number represent a toxic concentration or is it within the accepted therapeutic range? Can the level found be considered to be either the cause of death or contributing to it? Does the concentration found have any significance whatever?

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Contributors to the literature of drug analysis in its various aspects—forensic, drug abuse, clinical emergencies and therapeutic monitoring—have been most industrious. This overview of the evolution of techniques, the instrumentation and mechanisms and the art may profit the neophyte and perhaps even refresh the more expert.

October, 1976

E. Berman

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CHAPTER 1

WHAT IS DRUG ABUSE?

Drug abuse is a term applied to the questionable use by society of various chemical compounds classed as drugs. Misuse would be a more apt and descriptive term for the overall activity.

Man's use and misuse of these substances is not a modern entity and is not necessarily an alarming symptom of society's current social and moral decadence. Since his beginnings man has sought means to alleviate pain and to escape, momentarily, from the challenges and frustration of his environment. True, modern man has a greater variety of agents to use for therapeutics or indulgence than his ancestor had.

Alcohol, opium and hashish (marihuana) have been known since antiquity. These behaviour altering drugs have been used by many cultures as medicines and as a means of indulgence. As man explored and colonized, he carried these with him.

The Chinese *circa* 2700 B.C. are said to have employed marihuana for treating ills as diverse as gout, constipation and absent-mindedness. Some peoples gave hashish to warriors before a battle.

The Egyptians around 1500 B.C. recorded medicinal uses of opium. We are all familiar with the reference to opium addiction in Homer's *Ulysses*. By the beginning of the Christian era, opium was known in various parts of Europe.

Hallucinogens, obtained from various plants, were used intermittently and under controlled conditions by some primitive societies. Remnants of the practice can be found today among the Mexican Indian and adjoining tribes in southwest United States who still use peyote, a mushroom of the area containing the hallucinogen mescaline, to produce hallucinations during religious rites. Men of the Koryak tribes of Northeastern Asia and Siberia occasionally indulge in the hallucinogenic properties found in the mushroom *amanita muscaria*. Certain nomadic aborigines in Australia chew pituri, a preparation made from the leaves of a shrub belonging to the potato family. The active principle is

scopolamine. A related plant, *datura strammonium*, is used among South American Indians.

For most of the general public the term *drug abuse* implies addiction to the so-called 'hard drugs', i.e. morphine, cocaine, amphetamine, etc. by a relatively small, rather questionable, segment of society. In truth it is the prescribed and proprietary drugs which constitute the real 'drug abuse' problem. Four out of every five drug preparations, analgesics, cold remedies and sleeping compounds, which are used indiscriminately by the laity can be purchased legally without prescription. The modern physician, who, like his predecessor, tends to over-prescribe, compounds this situation further.

Patterns of drug abuse or misuse do not remain static. They are governed by factors such as availability, economic status of users and ignorance among both the lay public and clinician regarding the possible implications of indiscriminate use of various substances. For example, despite the extensive medical use of crude opium preparations and the purer drugs codeine and morphine, the medical profession of the nineteenth century did not fully appreciate the addictive liability of these drugs. To illustrate further, during the American Civil War these preparations were administered not only to the men wounded in battle, but also in quantity to those suffering from dysentery. As a result, vast numbers of soldiers were returned to civilian life addicted to morphine. The term 'soldier's illness', quite prevalent at that time, referred to narcotic addiction.

Of course narcotic abuse was not limited to the military populations. Among the prominent and gifted misusers of opium in the nineteenth century were the American writer Edgar Allan Poe, the English poet Samuel Taylor Coleridge and the Russian composer Moussorgsky. Probably the most famous opium addict of that century was Thomas de Quincy, the author of 'Confessions of an Opium Eater'. Addicts, then, were older individuals than those of the present.

As in our era, nineteenth century writers discussing the magnitude of the drug problem blamed 'the times and the tensions'. A few, however, charged that physicians prescribed narcotics indiscriminately.

Today, numerous additional compounds are available for therapeutic use and misuse and for self-medication. The first barbiturate barbital (veronal) was introduced by Fischer and von Mesing in 1903. Initial investigations of amphetamine were reported in 1930. Since World War II, the drug manufacturer has been most industrious in creating new compounds and in developing their market. Chlorpromazine was introduced in 1952, propoxyphene in 1953, and diazepam appeared in 1961.

Major drugs of misuse at any one time are prescription drugs being dispensed frequently or proprietary preparations forced into the public's attention by the advertising media. In the late 1940s apparent overdose cases admitted to hospitals involved bromides or salicylates, primarily. Alcohol, then as now, was an additional toxic agent to be considered. Barbiturates were a rare problem then, but in the 1950s and 1960s barbiturate use increased markedly. One also

saw phenothiazine and propoxyphene overdose, not too infrequently. Amphetamine misuse (emanating from 'diet pills') was also being encountered.

In the late 1960s, the more sophisticated analytical procedures then implemented routinely, indicated that multiple drugs were being misused, simultaneously. This practice rather challenges the expertise of both clinician and analyst.

Currently, diazepam abuse is competitive with that of barbiturates. The use of methaqualone, so prevalent about a year ago, seems to be on the wane. Acetaminophen, resurrected from an older pharmacopeia, appears to be competitive with acetyl salicylate as an analgesic and as a subject of drug misuse.

It should not be too surprising that economic status influences drug abuse patterns. All drugs, legal and illicit, are costly. For example, during the LSD era of the 1960s, its use among young people in the ghetto areas of Chicago was minimal. They took their 'trips' with 'Dr Schiffman's Asthmador', a proprietary first compounded in 1890 for the relief of asthma; its active ingredients, *datura strammonium* and ephedrine. A teaspoonful in a glass of Coca Cola assured a twenty-four hour trip at least. To illustrate further, the use of hard drugs (morphine, cocaine, amphetamine) seems to have declined somewhat among the teenagers and young adults in disadvantaged areas but is reported to have increased significantly in the more affluent suburbs. Marihuana use is more prevalent.

Discretion is indicated when comparing the apparent degree of present drug misuse with that of the past. First of all both the practicing physician and the lay public are more aware of the implications of improper drug use. Therefore, toxicological analyses are frequently performed in clinical areas for miscellaneous reasons. Also many forensic laboratories investigate the presence of drugs routinely, even though a death from other causes has been established. Because of advances in technology, routine toxicological analyses are more exhaustive than in the past. Thus, more components may now be uncovered. Adequate knowledge regarding the pharmacology of specific substances and the significance of concentrations found to be present may eliminate misinterpretations. A drug found in a certain investigation, clinical or forensic, may be present for therapeutic reasons only.

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CHAPTER 2

CLASSES OF COMPOUNDS CALLED DRUGS

Before substances involved in probable toxicological situations can be identified and quantitated by chemical and/or instrumental means, they must first be isolated from their respective matrices, i.e. blood and other biological fluids, different tissues, plant materials, miscellaneous foodstuffs, various liquids, ointments, salts, powders, pills, capsules, etc. The choice of analytical methods applied is governed by the nature and quantity of the materials being investigated, the nature of the toxic agents suspected, instrumentation and general equipment available. For the analyst, it is convenient to group different chemical substances according to basic procedures used to isolate them. Major classifications employed frequently include: (i) inorganic substances that can be isolated from matrices by wet or dry ashing, dialysis, protein precipitation, chelation and solvent extraction; (ii) volatile agents isolated by distillation or diffusion techniques and (iii) organic compounds extractable from aqueous solutions by immiscible (organic) solvents.[1-3]

Compounds of interest are contained in the latter two classes, primarily. Ethyl alcohol, a volatile substance, has been a major drug of misuse since the beginning of time. A few drugs like amphetamine or nicotine can be isolated by both distillation and solvent extraction.

About the only inorganic substance employed as a drug and thus misused is sodium bromide. It has enjoyed considerable popularity as a hypnotic and as an antiepileptic agent.

There is no single all purpose procedure for isolating all drugs which are extractable from aqueous solutions. Various compounds behave differently; some as acids, others as bases and a number are amphoteric. For convenience in setting up analytical schemes, organic compounds, then, are classified as acidic, neutral or basic substances.

To elucidate further, acidic drugs may be extracted from acid aqueous solutions (pH below 7) by organic solvents; these form water soluble alkali salts, i.e. with sodium, potassium, calcium.

Basic drugs, in general, are extracted from alkaline aqueous solutions (pH above 8) by organic solvents. These form acid salts. However, a number of basic drugs including aconitine, cocaine, most antihistamines, meperidine, methadone and some phenothiazines form hydrochloride salts which are chloroform soluble, i.e. these specific basic drugs are chloroform extractable from weak hydrochloric acid solutions. Chloroform also extracts strychnine as a sulphate from aqueous solutions at pH 4·5.

TABLE 2.1
Representative acidic drugs

Drug	Classification	Drug	Classification
Acetazolamide (Diamox)	Diuretic	Diphenylhydantoin	Anticonvulsant
Aloin	Purgative	Phenylbutazone	Analgesic
Barbiturates	Hypnotic	Pyrimidone	Anticonvulsant
Bemegide	Central Stimulant	Salicylates	Analgesic
Chlorothiazide	Diuretic	Sulfonamides	Antimicrobial agent
Cyclothiazide	Diuretic	Warfarin	Anticoagulant/ Rodenticide

Neutral drugs are extractable from either acidic or basic solution. In actual practice it is preferred to remove these substances with the acidic group since that fraction contains fewer drugs. The separation of individual components is then easier.

There is a small group of very water soluble-solvent insoluble drugs that remain in the aqueous fraction after all other groups have been extracted. Choline drugs, quaternary ammonium compounds and insulin are representative of these.

TABLE 2.2
Representative neutral drugs

Drug	Classification	Drug	Classification
Acetaminophen	Analgesic	Meprobamate (Equinil, Miltown)	Tranquilizer
Acetanilide	Analgesic	Methsuximide	Anticonvulsant
Aminopyrine	Analgesic	Methyprylon (Noludar)	Hypnotic
Aminosalicylic acid (PAS)	Tuberculostatic	Nikethamide	Central stimulant
Caffeine	Mild stimulant (tea, coffee)	Phenacetin	Analgesic
Carbromal	Hypnotic	Theobromine	Xanthine derivative (cocoa)
Ethinamate	Hypnotic	Theophylline (aminophylline)	Muscle relaxant, antiasthmatic
Ethosuximide	Anticonvulsant		
Glutethimide (Doriden)	Hypnotic		

Clarke[2] suggests acidifying the aqueous fraction remaining, evaporating to dryness and extracting the residue with methanol. Tompsett[4] isolated antihypertensive drugs from biological materials by cation-exchange chromatography.

Representative acidic, neutral and basic drugs together with their pharmacologic classification are listed in Tables 2.1–2.3.

TABLE 2.3
Representative basic drugs

Drug	Classification	Drug	Classification
Acepromazine	Tranquilizer	Meperidine (Pethidine)	Analgesic (narcotic)
Acetophenazine	Tranquilizer		
Aconitine	Depressant, diaphoretic	Mepivicaine	Local anesthetic
		Mescaline	Hallucinogen
Amitriptyline	Antidepressant	Methadone	Analgesic (narcotic)
Amphetamine	Central stimulant	Methapyrilene	Antihistamine
Antazoline	Antihistamine	Methaqualone	Hypnotic
Atropine	Parasympathetic	Methylphenidate	Central stimulant
Benzoyl ecgonine	Cocaine metabolite	Morphine	Analgesic (narcotic)
Bufotenine	Hallucinogen	Nalorphine	Narcotic antagonist
Butacaine	Local anesthetic	Nicotine	Ganglionic blocking agent
Carbamazepine	Anticonvulsant		
Chlorcyclizine	Antihistamine	Nortriptyline	Antidepressant
Chlordiazepoxide (Librium)	Tranquilizer	Orphenadrine	Parasympatholytic
		Oxazepam	Tranquilizer
Chloroquine	Antimalarial	Pamaquin	Antimalarial
Chlorpromazine	Tranquilizer	Papaverine	Antispasmodic
Cinchonine	Antimalarial	Pentazocine	Analgesic
Cocaine	Local anesthetic	Perphenazine	Tranquilizer
Codeine	Analgesic	Phencyclidine	Analgesic/ anesthetic
Cyclizine	Antihistamine		
Dextromethorphan	Antitussive	Phenindamine	Antihistamine
Diazepam	Tranquilizer	Phenmetrazine	Anorectic
Diphenhydramine	Antihistamine	Phenylephrine	Sympathomimetic
Doxylamine	Antihistamine	Phenylpropanolamine	Sympathomimetic
Emetine	Antiamoebic	Phenyramidol	Analgesic
Ephedrine	Sympathomimetic	Physostigmine	Anticholinesterase
Ergotamine	Adrenergic blocking agent (use—migraine)	Procaine	Local anesthetic
		Prochlorperazine	Tranquilizer
Fluopromazine	Tranquilizer	Propranolol	Cardiac depressant
Fluphenazine	Tranquilizer	Quinine	Antimalarial
Hydralazine	Antihypertensive	Quinidine	Myocardial depressant
Imipramine	Antidepressant		
Iproniazid	Antidepressant	Reserpine	Antihypertensive
Isoniazid	Tuberculostatic	Salicylamide	Analgesic
Lidocaine (Lignocaine)	Local anesthetic	Scopolamine	Parasympathetic
		Strychnine	Central stimulant
Lysergic acid (LSD)	Hallucinogen	Thioridazine	Tranquilizer
Mepazine	Tranquilizer	Thonzylamine	Antihistamine

Chloroform and/or ether are the immiscible solvents employed most commonly in drug analyses. When only a single drug is being determined in a specimen a solvent found to be most efficient for that specific purpose is used. For example, ethylene dichloride (1,2-dichloroethane) is the preferred solvent for extracting out salicylates. Chloroform alone is not too effective in removing chlorothiazide from acid aqueous solutions but a 20:80 mixture of isobutanol: chloroform is fairly effective. There are other examples.

CHAPTER 3

EVOLUTION OF DRUG SEPARATION TECHNOLOGY

The development at the beginning of the nineteenth century of processes for separating fairly pure alkaloids from their plants presented to the toxicologist of that era a means by which alkaloids could be separated from the animal body and subsequently identified. The basic methodologies then devised are still applied today, with some modification, in both forensic and clinical toxicological analyses.

In 1851 Stas introduced a procedure which consists of first treating the material with strong alcohol, acidified with tartaric or oxalic acid, then, warming same, cooling and filtering. The residue remaining after evaporation of the filtrate is dissolved in water, gradually alkalinized with sodium or potassium carbonate and extracted with ether.[5]

In 1856 Otto modified Stas' method by agitating the acidic filtrate with ether, to remove fats, prior to attempting extraction of alkaloids from an alkalinized filtrate. Ammonium chloride was added to precipitate any morphine present. Amyl alcohol was the extracting solvent.[6]

Various investigators of that time preferred to use chloroform as the extracting solvent.

The procedure published by Dragendoff in 1866 is most elegant. He first extracted materials with water acidulated with sulphuric acid and concentrated the extract. The concentrate was then mixed with strong alcohol and, after standing for twenty-four hours, was filtered cold. Following distillation of the alcohol, the aqueous solution remaining was shaken in turn with petroleum ether, benzene, chloroform and petroleum ether, to yield fractions I, II, III, IV. The aqueous solution was alkalinized and re-extracted in turn with petroleum ether, benzene, chloroform and amyl alcohol to yield extracts V, VI, VII, VIII. The alkaline aqueous liquid remaining was mixed with powdered glass, evaporated and extracted with chloroform to give extract IX. Each fraction was examined separately for different organic poisons.[7]

Kippenberger's process published in 1895 is based on the formation of soluble alkaloidal compounds and insoluble protein precipitates following 'digestion' of materials with glycerol and tannic acid. The resulting mixture is then extracted with acidulated water and treated much as described in earlier procedures.[8]

Other precipitation methods of the time depended upon the formation of insoluble alkaloidal compounds which were subsequently isolated.

Witthaus, about 1906, presented a method that combined various features from existing procedures with a few innovations of his own.

Separations achieved as described contained miscellaneous biological components as well as the drugs of interest. Occasionally dialysis was employed as a means of separating alkaloids from tissue proteins. However, the separations so achieved were not found to be significantly cleaner than those obtained with extraction methods.

A procedure based upon the absorption of alkaloids in solution onto freshly burned animal charcoal and their subsequent release into boiling alcohol was advocated by a few workers. Alkaloids in the residue remaining after distilling off the alcohol were then extracted out by the preferred solvents. This procedure known as the Graham-Hofman method was first adopted for the analysis of strychnine in beer.[8] Possibly, it represents the first recorded application of a chromatographic principle to toxicological analysis.

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