A.3 AMPHETAMINES AND AMPHETAMINE-LIKE DRUGS

INTRODUCTION

Amphetamines are synthetic amines which are in some ways similar to the body's own adrenalin (epinephrine). These drugs generally evoke an arousal or activating response not unlike one's normal reaction to emergency or stress. Naturally occurring stimulants, such as khat, ephedrine, strychnine, cathine, caffeine and cocaine, have been used in various cultures for centuries.[18, 139] Amphetamines were first synthesized in the latter part of the 19th century, although their major pharmacological properties were not discovered until 1928.[2, 42]

A variety of amphetamine-related drugs currently exist. The most common amphetamine substances are amphetamine (Benzedrine®), dextroamphetamine (Dexedrine®), and methamphetamine (Methedrine® or Desoxyn®), with Benzedrine® being the least potent. Pharmacologically similar ("amphetamine-like") drugs with different chemical structures include benzphetamine (Didrex®), phenmetrazine (Preludin®), phendimetrazine (Dietrol® or Plegine®), methylphenidate (Ritalin®), pipradrol (Meratran®), diethylpropion (Tenuate®, also called amfepramone), and chlorphenteramine (Pre-sate®). Although various distinctions can be drawn among these drugs, many of their effects are similar if the dose is adjusted, and, consequently, they will be discussed as a group, with amphetamine as the prototype. Two amphetamine-related drugs, MDA (methylenedioxyamphetamine) and STP (DOM or dimethoxymethylamphetamine), with potent psychedelic-hallucinogenic properties are discussed in A.5 *Hallucinogens.* Cocaine is dealt with separately below. (See A.4 *Cocaine.*) Caffeine is not discussed in detail in this report, but the reader is referred to several recent reviews of the effects of this popular drug.[h] Common slang terms for the various amphetamines and amphetamine-like drugs include: 'speed', 'crystal', 'meth', 'bennies', 'dexies', 'A', 'uppers', 'go fast', 'pep pills', 'diet pills', 'jolly beans', 'truck drivers', 'co-pilots', 'eye openers', 'wake-ups', 'hearts' and 'footballs'.

Amphetamines were introduced in medicine in the 1930s, and their stimulating properties were widely used by both Allied and Axis soldiers during World War II to counteract fatigue. Since then, amphetamines have been commonly employed in medical practice and often used non-medically by vehicle drivers on long trips, night-shift workers, fatigued housewives, students studying for exams and others who must meet deadlines, athletes attempting to increase performance, and others desiring general stimulation, pleasure or fun.

In the late 1940s much of the war-time drug stockpile became available on the world market, and in many countries amphetamines were available on a non-prescription, over-the-counter basis. Widespread use followed in most industrialized areas with numerous unpleasant consequences. Use reached epidemic proportions, for example, in the 1950s in Japan—a country

which had never previously had a serious drug problem except alcoholims.[20, 100] Since this time, amphetamines and related drugs have generally been put under governmental control, and in some countries, such as Sweden, they are highly restricted in both medical and non-medical applications. Additional controls on the medical use of amphetamines and some related drugs have recently been imposed in Canada as well.[23]

The popularity of medical and non-medical use of these drugs spread rapidly in all age groups and social classes in North America after W.W. II. The drugs were usually taken orally or sniffed, and, more rarely, injected. Oral use was made of 'dismantled' Benzedrine® inhalers, which were on the unrestricted legal market at that time.

Popular oral use of amphetamines has continued, and in the mid-1960s a phenomenon new to North America developed and has caused major concern—the intravenous use of massive doses by persons commonly referred to as 'speeders' or 'speed freaks'. In North America, methamphetamine has been the most popular substance for such use, but in other countries, such as Sweden,[12] phenmetrazine is preferred. Although this practice has been most frequently noted among youthful multi-drug-taking individuals, considerable opposition to such use of amphetamines has developed with the 'hip' community. The 'speed trip' is in many respects the antithesis of the experience sought with psychedelic drugs. Instead of the orientation towards the 'consciousness expansion', personal insight, and aesthetic and religious awareness often attributed to the psychedelic drug experience by hallucinogen users, the 'speed' phenomenon is usually characterized by action, power, arrogance and physical pleasure, and regularly leads to suspicion, paranoia, hostility and, often, aggression and violence. In addition to these undesirable personal characteristics, which often render 'speed freaks' highly unpopular, even amongst their peers, 'speeders' generally present a picture of chronic ill health unparalleled among other youthful users.

The message received by the Commission at public and private hearings, and in written communication with youthful drug users has been mostly negative towards 'speed'. Many experienced illicit drug users consider amphetamines extremely dangerous and undesirable, and have expressed surprisingly hostile attitudes toward these drugs in no uncertain terms. Numerous persons well known to youth, who have had considerable influence on drug attitudes during the past decade (e.g., John Lennon and the Beatles, Frank Zappa and the Mothers of Invention, Timothy Leary, Allen Ginsberg, and Donovan) have made public statements against the use of 'speed'.

Amphetamines are legally available in a variety of tablets, capsules (both in immediate and delayed release forms), elixirs, liquid injections and, until recently, inhalers.[121] Methamphetamine generally appears in powder or 'crystal' form on the illicit market. Amphetamines have been available for medical use in North America in combination with such drugs as barbiturates (e.g., Dexamyl®) and other sedatives, atropine, caffeine, vitamins and

minerals, and thyroid extract. One of the most exotic pharmaceutical combinations has been described as follows:

> This is a multi-coated tablet of pentobarbital on the outside to induce sleep rapidly, phenobarbital under a delayed dissolving coating to extend the sleep, and under another coating, an amphetamine to awaken the patient in the morning.[96]

As with other prescription drugs which are widely used, such as the barbiturates, minor tranquilizers and related sedatives, the distinction between medical and non-medical use of amphetamines is not always easily made.

Medical Use

As early as 1935, amphetamines (in oral doses from 20–200 mg per day) were found to be a specific treatment for narcolepsy, an uncommon illness which is characterized by sudden attacks of weakness and sleep. These drugs remain the most effective treatment for this disorder.

Since the 1940s amphetamines (generally in doses of 10–50 mg per day) have been used in the treatment of overactive children who showed disorders of attention and impairment of learning capacity. In the last few years, a number of investigators have published results of controlled studies which revealed that amphetamines and methylphenidate were among the most effective treatments for hyperkinetic disorders. There has been a considerable amount of controversy surrounding the use of stimulants in the management of overactive children. Some opponents claim that the drugs are frequently used for social rather than medical reasons to make unruly children conform to the standards of an overly discipline-conscious school system.[40, 70, 91, 117]

Psychiatrists have occasionally used intravenous injections of methedrine (in doses of 15–30 mg) for diagnostic purposes. Administered in this fashion, the drug induces a state of excitation, elation and increased talkativeness, during which a previously inhibited patient may reveal information and symptoms which might be considered important for the understanding of his disorder. He may also express, more freely, previously suppressed emotions. It has been observed that some patients with a border-line psychosis show typical psychotic symptoms more clearly following an injection of amphetamines.

At one time, these drugs were tried in the treatment of alcoholism and opiate narcotic dependence, but this practice was not successful and was abandoned. Since drug dependence is often a chronic condition, some patients who took this treatment became dependent on amphetamines instead of, or in addition to, their original drug.

Early hopes that amphetamines would prove to be an effective general treatment for severe depression were soon disappointed. Although these drugs are powerful stimulants and increase a depressed person's activity, they may also make him more anxious and agitated, deprive him of sleep,

and may fail to elevate his mood or to reverse the fundamental depressive process. In some well-selected individuals, amphetamines have been effective in relieving mild depression and chronic fatigue. Other drugs which do not have significant stimulant-euphoric properties, such as phenelzine (Nardil®), amitriptyline (Elavil®) and imipramine (Tofranil®) are generally recommended for the chemotherapy of severe depression.

Amphetamines have a strong anorectic or appetite-suppressing effect. Most so-called 'diet pills' contain amphetamines or similar preparations. However, the appetite-suppressing action together with the pleasant stimulating effects of these drugs usually declines after about two weeks of regular use, unless the dose is continuously increased. Weight loss so produced has often been only temporary, and amphetamines are no longer generally recommended for the treatment of obesity. Fenfluramine (an amphetamine analog) suppresses appetite without producing general stimulation effects and has recently been approved for medical use in Canada. (The potential for non-medical use of fenfluramine has not been extensively studied.)

Recent regulations in Canada restrict the regular medical use of amphetamines, phenmetrazine and phendimetrazine (but not other amphetamine-like drugs) to the treatment of narcolepsy, hyperkinesis, mental retardation, epilepsy, parkinsonism, and hypotensive states associated with anesthesia.[23] Amphetamines have also been used, with varying degrees of success, in the treatment of pregnancy nausea, asthma, nasal congestion, nocturnal enuresis (bet wetting), pain and sedative overdose.[75, 92, 98]

Chemical Analysis of Illicit Samples in Canada

Methamphetamine is the most common of the stimulant drugs noted in reports of police seizures and 'street drug' analyses in Canada. Other amphetamines and amphetamine-like drugs are occasionally noted, but relatively few such samples have been identified chemically. When found, these latter drugs are typically of high quality and generally were originally produced by legitimate manufacturers. The methamphetamine available on the illicit market is usually prepared in clandestine laboratories and is apparently often misrepresented or of poor quality, contaminated by products of faulty and incomplete synthesis, and may be mixed with other drugs. As with other drugs, alleged amphetamine samples submitted to Canadian laboratories for analysis are often those suspected of being adulterated, some unknown drug, or the cause of adverse reactions. Consequently, the samples reviewed in the following section cannot be considered a representative selection of illicit Canadian amphetamines.

In the Marshman and Gibbins 1970 study of illicit drugs collected in Ontario, 70 samples were presented to the researchers as methamphetamine. Of these, 61.4% actually contained the drug.[99] In addition, methamphetamine was detected in five samples which were alleged to be other substances. Amphetamines were found mixed with other drugs in only two instances.

Gibbins found that methamphetamine samples sold as grams (i.e., 'street grams') on the illicit market in Toronto typically contained less than one-tenth the specified quantity of the drug.[50]

The Commission's national survey of 'street drug' analysis facilities covering 1971–72 and our own collection of drug samples provide data on 86 items alleged to be primarily methamphetamine.[106, c] Of these samples:

35% were methamphetamine
38% contained methamphetamine and other drug(s)
20% were some other drug(s)
7% contained no drug

Of nine additional samples presented as methamphetamine mixtures, only five contained the drug and none of the combinations were as alleged. Of a total of 111 methamphetamine-containing samples found in the study, 62 (56%) were relatively pure and free of adulteration. The most common mixtures found contained other amphetamines, barbiturates, LSD or PCP, but no one combination occurred more than a few times. In addition, 22 samples containing other amphetamines and 2 of phenmetrazine were found. Approximately one-half of these were mixed with other drugs. Most had been represented as methamphetamine. Methylphenidate was not detected in any samples.

The Health Protection Branch has reported to the Commission the quantitative analysis of 286 samples containing methamphetamine which were seized by the police during the period of June 1971–October 1972.[63, b] Many of these samples had been selected for special analysis because of previously detected impurities and consequently cannot be considered representative of either the forms of the drug on the street or of police seizures in general. These samples were almost exclusively in bulk powder or 'crystal' form (as opposed to capsules or tablets) and ranged from 0.6% to 97.2% pure methamphetamine with a median of 39.2%. Products of faulty or incomplete synthesis were often found, as were other amphetamines. No other impurities or specific mixtures occurred more than a few times each in this collection.

Administration, Absorption, Distribution, and Physiological Fate

Amphetamines are usually administered orally and are readily absorbed from the gastrointestinal tract. Occasionally, intramuscular or intravenous injections are used medically. In the past, an amphetamine base inhaler was also available. Amphetamine can be smoked if it is burned with some combustible material such as tobacco. Non-medical users may employ any of these administration routes, including sniffing 'crystal'. Chronic 'speed freaks' generally prefer intravenous injections.

The various amphetamine-related drugs differ to a certain extent in the rate of metabolism and elimination, but the general processes are similar. About half of the amphetamine which enters the body is excreted unchanged in the urine; the remainder is metabolized or chemically altered in the liver prior to elimination. Excretion of the bulk of the dose is rapid, but traces of the drug may be found in the urine up to a week after the last administration.[14, 75, 92, 98] Because of the considerable proportion excreted unchanged, certain persons have been reported to extract and re-use crystals from the urine when fresh supplies were scarce. (This general practice of 'reclaiming' excreted drugs is not new, and such procedures have been recorded for centuries.)

Amphetamines and metabolites can be readily identified in blood and urine using standard techniques. Most other popular stimulants are also detectible in body tissue and fluids.[9, 29, 80, 107, 137] Extremely sensitive and rapid immunoassay techniques have recently been developed for the analysis of amphetamines.[96]

Moderate Dose Effects[31, 75, 92, 98]

Both the psychological and physiological responses to amphetamines vary profoundly with dose, and the acute effects of intravenous injection may differ significantly from oral doses. The general effects vary continuously over the full dosage range, but for clarification in the following discussion, the oral use of moderate quantities of amphetamines will be separated from high-dose oral and intravenous use.

At typical therapeutic doses (e.g., 5–30 mg) amphetamines produce electrophysiological (EEG) signs of central nervous system (CNS) activation, along with a variety of adrenalin-like peripheral (sympathomimetic) effects such as increased blood pressure, pulse rate and blood sugar; slight dilation of some blood vessels and constriction of others; widening of the pupils; increased respiration rate; depression of appetite; and some relaxation of smooth muscle. Such effects might last three to four hours.

The psychological response varies among individuals, but might typically include increased wakefulness, alertness, and vigilance, improvement in concentration and a feeling of clearer thinking, decreased fatigue and boredom, elevation of mood, a feeling of sociability, increased initiative and energy, and increased verbal and other behavioural activity. There may be an improvement in some simple mental tasks, in reaction time and muscular coordination, and in athletic performance. In general, improved functioning is most likely to occur when prior performance was at a sub-normal state due to drowsiness, fatigue or boredom.[39, 147]

On the other hand, a moderate dose of amphetamine in other individuals (or perhaps even in the same individual at different times) might produce irritation, inability to concentrate, restlessness, anxiety, confusion, depersonalization, insomnia, blurred vision, tremor, nausea, headache, dizziness, heart palpitation, drowsiness, chest pains, chilliness, urinary retention, diarrhea or constipation, and other adverse symptoms. With higher doses, hypersensitivity, delirium, panic, aggression, hallucinations, psychosis, and cardiovascular abnormalities may occur in some individuals. There does not appear to be any evidence of irreversible physiological damage associated with long-term use of moderate doses of amphetamines, although temporary disorders do occur. Although deaths are rare, some fatalities have been reported in the literature in unusually sensitive individuals.[82]

After continued administration of even moderate doses, withdrawal may be associated with fatigue, drowsiness and, not infrequently, emotional depression. The increased energy and alertness elicited by the drug merely postpone the need for rest and clearly provide no long-term substitute for it. Many regular users of stimulants rely on these drugs for energy when fatigued and often do not get proper rest for long periods of time.

It has frequently been said that amphetamines have a "paradoxical effect" on children, especially in cases of hyperkinesis. These drugs reportedly calm hyperactivity and improve school performance in some unruly youngsters, but are considered CNS stimulants in adults. However, the reports are not necessarily contradictory since amphetamines are often noted to enhance concentration and directed attention and to reduce boredom in adults, as well as children, and may not necessarily lead to increased general motor activity in either case. The repetitive, obsessive-compulsive behaviour often seen with high-dose amphetamine use (to be discussed below) may involve pharmacological mechanisms analogous to those producing therapeutic effects on hyperkinetic children at lower doses.

High-Dose Effects

There has been little direct experimental investigation on the effects of high doses of amphetamines in humans. The chronic, high-dose intravenous amphetamine syndrome has been described by numerous authors.[27, 44, 90, 124] A similar picture may exist with high-dose oral or nasal use as well.[82] The cycle or pattern of use usually begins with several days of repeated injections (usually of methamphetamine) gradually increasing in magnitude and frequency. Some users may 'shoot' or 'crank' up to several 'street grams' in a single day.[55, 90, 131] (As noted earlier, however, the actual doses employed are uncertain, and it is unlikely that they exceed a few hundred milligrams.) Initially, the user may feel energetic, talkative, enthusiastic, happy, confident and powerful, and may initiate and complete highly ambitious tasks. He often becomes involved in behaviour of a repetitive, compulsive nature (called "punding" in Sweden). He does not sleep and usually eats very little. After

the first few days, however, unpleasant toxic symptoms become stronger, especially as the dose is increased. These toxic effects may be similar to those described earlier for lower doses but appear in amplified and exaggerated form. Some symptoms commonly reported at this stage are: compulsive and stereo-typed repetition of meaningless acts, automatic jerking movements, irritability, self-consciousness, suspiciousness, fear, hallucinations and delusions which may take on the characteristics of a severe paranoid psychosis. Aggressive and antisocial behaviour may occur at this time. A number of homicides have been reported to result from such paranoia.[43] Hallucinations often include tingling, itching and creeping sensations under the skin thought to be caused by insects or parasites. Intense scratching or digging at these imaginary 'crank bugs' may become so intense as to produce bleeding sores and permanent scars. Severe chest pains, abdominal pain mimicking appendicitis and unconsciousness lasting an hour or more have also been reported after 'over-amping', or injecting too large a dose.[89, 132]

Towards the end of the 'run' (usually less than a week) the toxic symptoms dominate, the drug is discontinued, fatigue sets in, and prolonged sleep follows, sometimes lasting several days. Upon awakening, the user is usually lethargic, ravenously hungry and often emotionally depressed. The user may overcome these effects with another injection—thus initiating the cycle anew. In other instances, 'runs' may be separated by days or weeks. On certain occasions, 'down' drugs, such as barbiturates or minor tranquilizers, and more recently, opiate narcotics may be used to 'crash' or terminate a run which has become intolerable or otherwise unpleasant.

'Speed freaks' are generally unpopular within the multi-drug-using community and are often shunned. Consequently, these individuals may live together in 'flash houses' totally occupied by amphetamine users. Frequent 'hassles', aggression and violence have been reported in such dwellings. Heavy users are generally unable to hold a steady job because of the drug use patterns and often develop a parasitic relationship with the rest of the illicit drug-using community. There are reports that many chronic users support themselves through petty crime.[13, 115] There is significant evidence that much of the violence and criminal behaviour associated with 'speed' use may reflect social and pre-existing psychological conditions as much as the pharmacological effects of the drug.[133]

The immediate effect of the intravenous injection of amphetamines is a sudden, overwhelming pleasurable 'rush' or 'flash' which has been described by users in such terms as "an instant total body orgasm". This effect is reportedly quite different from the warm, drifting sensation associated with opiate narcotics injection, but may be initially similar to the 'splash' produced by intravenous cocaine.[27, 90, 131] Some users claim that the immediate fantastic pleasure of the injection is their prime motivation for using 'speed', and that other aspects are secondary. There are also reports of 'needle freaks', for whom the use of the hypodermic syringe has acquired special rewarding connotations beyond the actual pharmacological effects of the drugs. On the

other hand, since high-dose oral or sniffing use has been commonly reported in the literature for years, the injection 'rush' is clearly not a necessary component for all chronic users.[82] In addition, it has been reported that some kind of initial (but delayed) 'rush' may be produced by large doses taken orally.

Some individuals report that sexual activity is prolonged by amphetamines, and may continue for hours. When orgasm finally comes it may be more pleasurable than normal; however, some users describe an inability to reach a climax. While only a minority of users report increased sexual activity, some people give this reason as a primary one for taking the drug.[13, 36, 90, 124] Other users claim that they take the drug simply for euphoria or 'kicks', or because it enables them to be more confident and active.

The clinical picture of the chronic 'speed freak' is a distressing one indeed. Continued use of massive doses of amphetamines often leads to dehydration and considerable weight loss, sores and non-healing ulcers, brittle fingernails, tooth grinding, chronic chest infections, liver and cardiovascular diseases, a variety of hypertensive disorders, gastrointestinal dysfunction, psychiatric problems and, in rare cases, cerebral hemorrhage.[30, 52, 89, 90, 130, 148] The extent to which these effects are the direct result of the drug or the secondary consequences of poor eating habits and malnutrition, unhygenic living conditions, over-exertion and improper rest is unclear, but evidence of direct damage due to high-dose use is accumulating.[52, 83, 86, 122, 148] Necrotizing angiitis, a progressive inflammatory disorder of the small arteries, has been reported in a group of intravenous amphetamine users, with fatal outcome in some. This disease may be linked to the drug and is often fatal if untreated.[28] Further complications may be caused by unsterile and shared needles and injections, including tetanus, abcesses and ulcers of the skin, hepatitis, perhaps malaria, and a variety of other infections. Many problems associated with the injection of insoluble or colloidal particles often present in street 'speed' have been reported. Similar problems occur when tablets, legitimately produced for oral use only, are crushed, mixed with water and injected.[8, 128] Although users may strain the drug solution through a wad of cotton or a cigarette filter as they draw it into the needle for injection, such measures are generally inadequate for this purpose and may, in fact, add impurities.

Although some users feel certain that their mental abilities have been impaired by heavy use, no clear picture of irreversible brain damage as a regular effect in human users has appeared in the literature. Several investigators have suggested that recovery from the major effects of chronic 'speed' use is slow but rather complete, requiring perhaps 6–12 months of abstinence and favourable living conditions.[3, 89, 90] However, a recent study with monkeys, employing high doses within the range consumed by some chronic human users, revealed evidence of significant cardiovascular change and permanent neurological damage after only a few weeks of daily drug administration.[122] This is clearly a high priority area for further research.

The acute psychosis reportedly produced by heavy amphetamine use has received much attention recently. Many investigators contend that the condition is often indistinguishable from paranoid schizophrenia.[32, 45] Prolonged lack of sleep, as occurs during a 'speed' run, by itself, has been shown to produce psychotic-like conditions.[114] This led to the hypothesis that the entire amphetamine psychosis syndrome might be caused by general sleep deprivation or REM (rapid eye movement phase) sleep blockade. Although severe psychosis apparently occurs most often after heavy chronic use in previously unstable and perhaps pre-psychotic individuals,[10, 44, 45, 66, 69] symptoms of psychosis have been produced under controlled experimental conditions after less than two days of repeated administration in non-psychotic subjects.[6, 57, 58, 59] Prolonged sleep deprivation, then, is not a necessary component of an amphetamine psychosis,[46] although it probably plays a significant role in most instances. Phenothiazines seem to alleviate most of the signs of psychosis, and major symptoms generally clear up with proper rest after amphetamines are withdrawn. In some cases, however, residual symptoms may last for months after cessation of amphetamine use.[45]

The undoubtedly intricate causal relationships between prolonged psychiatric disturbances and chronic amphetamine use are not clear. While it is well established that high doses of amphetamines can reliably elicit or augment symptoms of psychiatric disorder as an acute effect, many investigators have stressed that a considerable degree of prior psychopathology often exists among regular 'speed' users—especially those who appear for psychiatric treatment.[10, 36, 44, 45, 66, 69, 82, 97] Links between the acute symptoms of amphetamine toxicity and long-lasting psychiatric conditions in chronic users must be further explored. It is often not apparent whether existing psychopathology has predisposed certain persons to heavy amphetamine use or if the drug itself has produced the prolonged behavioural disturbances frequently observed in chronic users. Considerable interaction among these variables is to be expected. As well, we have little epidemiological information as to the proportion of even heavy users who actually develop severe psychotic or other pathological conditions. Most studies of the psychological characteristics of amphetamine users have obtained subjects as a result of their contact with treatment or law enforcement facilities and, consequently, have limited generality.

Various local surveys of physicians reported to the Commission as well as our own studies confirm the notion that medical and related services in areas with a high incidence of 'speed' use are frequently called upon to treat amphetamine-related problems—both physical and psychological.[64, 67, 104, 109, 111, 120] Generally, little is done beyond acute detoxification. Hospitalization is apparently not common. (The Federal Poison Control Program Statistics are discussed below.)

In the Commission's 1971 national survey of psychiatric hospitals, amphetamines were mentioned as a primary or secondary factor in the diagnostic records of 68 (0.3%) of the 22,885 patients actually in residence

at that time.[67, d] In British Columbia, general hospitals with psychiatric wards were surveyed as well; amphetamines were noted in the diagnoses of 3 of the 293 psychiatric patients in the reporting institutions. In the national mental health data gathered by Statistics Canada, amphetamines were considered together with "other psycho-stimulants" (excluding cocaine) in a general category.[26, 118, e] Dependence on such drugs (ICD-304.6) was noted in the diagnoses of 176 (0.34%) of the first admissions and 95 (0.19%) of the readmissions to psychiatric hospitals and wards in Canada in 1970. Males outnumbered females by more than three-to-one in these data. It would appear that although various psychological and physical disorders are often noted in chronic amphetamine users, amphetamines are not presently a causal factor in a significant proportion of psychiatric hospital admissions in Canada. (See also Tables A.5, A.6 and A.7 in the Annex to this appendix.)

"Speed Kills"

In recent years, the slogan 'Speed Kills' has received much attention, and the idea appears to play a significant role in the attitude that some users and non-users have towards the drug. One commonly hears the view that once you're 'hooked on speed' you have only two to five years left to live. Some chronic 'speed freaks' incorporate this notion into the identity they present to others and the image they entertain of themselves. Many observers contend that the chronic use of intravenous amphetamines reflects a thinly disguised suicidal tendency, as well as an attention- and sympathy-gaining device. "Hello, I'm Philbert Desanex: I'm a speed freak and I'm going to be dead by fall," is only a slightly exaggerated caricature of the image purposefully projected by some of these individuals.

What is the evidence that 'Speed Kills' in the literal direct physical sense? Fatalities due to acute overdose are rarely documented.[82, 89] We have no reliable knowledge of the extent of heavy amphetamine use, and, although we hear many dire predictions, there is no adequate information on the long-term prognosis or outcome of such use. It would certainly appear, however, that chronic adherence to this practice can be most detrimental to the individual and, often, to those with whom he interacts.

Although there is little evidence that the life expectancy of 'speed freaks' is lower than others living under similar circumstances, many investigators suspect this to be so.[74] Suicide during the withdrawal phase has been cited as a risk.[32] While there are few cases in the literature of death directly attributed to chronic amphetamine use, Clement, Solursh and Van Ast mention "... a number of cases of death on the street [in Toronto] apparently related to high-dose amphetamine abuse. At autopsy, however, pathological evidence of death directly due to amphetamines is rare in such cases."[30] After a thorough review of the literature up to 1969, Cox and Smart of the Addiction Research Foundation reported: "Currently there is no evidence available on mortality rates among speed users and it is not certain that speed itself is a lethal drug. There is no evidence to support or deny that 'Speed Kills'."[35]

The Commission has investigated, in considerable detail, reports of amphetamine-related poisonings and deaths in Canada.[68, 105] The Federal Poison Control Program has records of approximately 600 toxic reaction or poisoning cases involving amphetamines or related stimulants in 1971.[108, f] Of these, 296 cases were attributed to 'speed', 115 to phenmetrazine, 51 to amphetamine, 38 to dextroamphetamine and 20 to methamphetamine. Two reports of amphetamine fatalities were noted. The proportion of these cases associated with intravenous use was not indicated. Slightly more than half of the individuals were 10 to 24 years of age, and approximately one-quarter of the cases involved children under five. Overall, two-thirds of the patients were males.

Four deaths in the country were ascribed to amphetamines in the Statistics Canada *Causes of death* 1971 report—two were young people, and two cases involved persons over 45 years of age.[25] After a search of records, the coroners of three provinces (Ontario, Alberta and British Columbia) provided the Commission with detailed reports of ten deaths thought to be related to the use of amphetamines during the years 1969–1971.[68, g] Only two cases were attributed directly to amphetamine poisoning or overdose. The remaining fatalities were due to hepatitis, gunshot wounds, and other accidents and suicides which were in some way associated with amphetamine use. All of these individuals were males, and eight were under 25 years of age. (Fatalities involving MDA are discussed in A.5 *Hallucinogens*.)

It would appear that even though large doses of amphetamines are physically toxic, these drugs rarely result in death as a direct acute overdose effect. Permanent consequences of chronic high-dose use on general physical condition, susceptibility to disease and overall longevity have yet to be fully clarified, but evidence is accumulating of detrimental effects in these areas.

Driving

As noted earlier, low doses of amphetamine typically result in a slight improvement in certain intellectual and perceptual abilities, reaction time and psychomotor performance. High or continuous doses likely result in detrimental effects on these functions, but there has been little direct experimentation in this regard. There is no available evidence that amphetamines have been a causal factor in a significant proportion of traffic accidents, although numerous anecdotes and case history reports have appeared in the literature. Evidence is accumulating, however, that under some conditions amphetamines may have detrimental effects on traffic safety, either through the direct effects of high doses or, indirectly, by preventing normal rest, facilitating overexertion and increasing driving exposure.[87, 112, 129, 145] Further research is needed in this area, emphasizing the chemical detection of drugs in body fluids and tissues of persons involved in traffic accidents.

Tolerance and Dependence

Tolerance to the various effects develops at different rates and to different degrees—some responses decline with chronic use sooner than others. The tendency to increase dose depends upon which of the potential drug effects is rewarding or reinforcing drug use. Many individuals, for instance, who use amphetamines to control narcolepsy may reach a stabilized dose and show very little need for increased quantity over a period of years. On the other hand, those using the drug to control appetite generally increase their dose since tolerance to the anorectic effect readily develops. Many psychological effects, such as the mood-elevating and stimulant response, may show a considerable sensitivity to tolerance, and individuals who either began using the drug to obtain these effects, or who acquired the taste for them after initially using amphetamines for other purposes, generally show a marked tendency to increase dose over time. Rapid tolerance reportedly occurs to the initial 'rush' following intravenous injection during a 'speed run'. Tolerance to some of the toxic properties occurs, and certain chronic users reportedly administer quantities which would be extremely toxic in a non-tolerant user. As with other drugs, the rate of tolerance development to the different pharmacological effects depends on the doses used, the frequency of administration, and various individual factors.[41, 71, 81, 90]

The question of physical dependence on amphetamines depends on the definition of the withdrawal symptoms necessary to meet the criterion. While it is clear that withdrawing amphetamine from chronic users does not produce as dramatic and physically distressing an abstinence syndrome as that associated with alcohol, barbiturates, or opiate narcotics, many investigators feel that the fatigue, prolonged sleep, brain wave (EEG) changes, voracious appetite, cardiovascular abnormalities, occasional gastrointestinal cramps, muscle aches and pains, lethargy and, often, severe emotional depression following the 'speed binge' constitute a physiological reaction analogous to the more dramatic withdrawal seen with depressant drugs.[32, 41, 77, 93, 113, 130, 146] As one 'speeder' told the Commission, "As high as you get when you're speeding, that's how low you get when you crash."

The tendency for tolerance-producing drugs to manifest a rebound type of physiological and psychological pattern upon withdrawal has been given considerable attention: amphetamine abstinence in chronic users is generally characterized by profound sedation and depression of mood and physiological function, while drugs such as alcohol, barbiturates and the opiate narcotics (all of which produce sleep in high doses) generally exhibit a withdrawal syndrome of severe and toxic overstimulation, in some instances to the point of convulsions.

The fact that amphetamines have a physically less intense withdrawal syndrome than most other dependence-producing drugs, clearly indicates that a profound physical dependence is not a necessary component in an overall severe drug dependency situation. Subjective psychological factors seem to

have considerably greater motivational importance in many instances—especially with chronic high-dose amphetamine use. While there is little evidence of any kind of physical dependence on moderate doses of amphetamines, psychological dependence on even low doses is frequently reported, and is considered by some to be a major hazard in both medical and non-medical use.

Amphetamines and Other Drugs

As noted earlier, amphetamines are sometimes used in conjunction or in alternation with a variety of depressant drugs such as barbiturates, tranquilizers, alcohol and opiate narcotics. The amphetamine and barbiturate 'up-down cycle' has been described in both youthful and 'respectable' adult users at a variety of doses. Amphetamines may intensify, prolong or otherwise alter the effects of LSD, and it is reported that the two drugs are sometimes mixed. In addition, it would appear that the majority of youthful 'speed' users have also had experience with marijuana and a variety of psychedelic and other illicit drugs, although many confirmed 'speed freaks' rarely consume hallucinogenic substances. Persons primarily dependent on opiate narcotics also frequently make use of stimulants such as amphetamine and, more rarely, cocaine—either as mixtures of the drugs or used separately on different occasions. In some instances, younger heroin users initially began opiate narcotics use secondarily as an aid or self-treatment for unpleasant aspects of chronic amphetamine use and subsequently went on to prefer heroin to 'speed'. (See also Appendix C *Extent and Patterns of Drug Use.*)

Interactions between opiate narcotics and amphetamine are complex. Physiological antagonism occurs with some responses, but not others.[78] It has been reported that amphetamines may enhance the pain-relieving properties of opiate narcotics when the two are administered together.[48] In addition, amphetamines and narcotics together may have significant antidepressant properties.[94] In rodent studies, cannabis has been shown to intensify amphetamine stimulant activity, but also to reduce acute amphetamine lethal toxicity.[49, 141] Interactions between amphetamines and drugs of the alcohol-barbiturate type are complicated. Under certain circumstances amphetamine may antagonize some of the effects of sedative drugs, including their lethal toxicity. In other areas however, the drugs may have additive effects. Amphetamines can reduce some of the symptoms of alcohol hangover.[7, 88, 103, 116, 127, 149]

Antagonists

Numerous compounds which antagonize various effects of amphetamine are currently being developed and investigated for possible use in the treatment of amphetamine dependence. Amphetamines produce a variety of central and peripheral effects and compounds which inhibit some responses may produce little change in others.

Alpha-methyl tryosine (α MT) has been shown to reduce the central stimulant and pleasurable subjective effects of intravenous amphetamine.[48, 62, 79, 135] In one recent series of studies employing intravenous doses of amphetamine (up to 200 mg), prior administration of 2 gm of α MT reduced self-rated amphetamine euphoria by 50%, and 4 gm almost eliminated the subjective effects entirely.[60, 61] The response to phenmetrazine was reduced as well. The duration of the amphetamine blockage was 24–48 hours. Tolerance to the antagonistic effects of α MT rapidly develops if it is administered daily, but significant tolerance does not occur (and amphetamine blockade is still maintained) if the drug is given in sufficient dose at two-day intervals. Other than some feelings of slight sedation, no major side effects with α MT were reported. There was no indication that the drug was interfering significantly with normal autonomic nervous system functioning. Further research on the effects of chronic high-dose α MT administration is needed.[1]

Other drugs which have been shown to block certain aspects of the amphetamine response include fenfluramine, methysergide and certain major tranquilizers such as chlorpromazine and pimozide (but not reserpine).[15, 46, 62, 89, 140, 144] The recent development of immunoassay methods for the detection of amphetamines in body fluid raises the possibility of using similar antibodies to inhibit amphetamine effects in the living organism.[96] However, immunization approaches to amphetamine antagonism could be complicated by the close chemical similarities between amphetamine and certain natural hormones in the body such as adrenalin.

Even if effective antagonists were found for the subjective effects of amphetamine that reinforce its use in humans, such compounds might well have no effect on the action of other readily available stimulants (such as methylphenidate), which have quite different chemical structures and possibly other mechanisms of action.[125]

A.4 COCAINE

Introduction

Cocaine is obtained from the leaves of *Erythroxylon coca,* a bush which is found in abundance in parts of South America. For more than a thousand years, the mountain Indians of Peru and Bolivia have chewed coca leaves for medical, non-medical and religious purposes. It is said that this practice provides renewed energy, endurance, and strength, reduces the need for food and water, improves the spirits, and helps the user withstand the discomforts of cold, illness, and fatigue. In the centuries before the Spanish invaded and conquered South America, coca played an important role in religious customs and ceremonies among the Incas.[6, 7, 34, 54, 57]

The coca leaf was brought to Europe from the New World by adventurers and tradesmen and it gained a considerable degree of popularity in

certain areas. In Paris, in the latter part of the last century, coca elixirs, lozenges and tea were commonly taken. Mariani's famous *Vin Coca Mariani,* made from an infusion of coca leaf and wine, was used and acclaimed by thousands, including Gounod, Pope Leo XIII and other European notables.[6, 35, 54] In the 1850s, cocaine, the principal active alkaloid in the coca plant, was isolated.[7, 27, 54] The natural leaf typically contains about one per cent of this material.

Among the first to inquire into the medical usefulness of cocaine was Sigmund Freud, later to become the father of psychoanalysis. In addition to his own extensive personal use of the drug, Freud recommended cocaine for the treatment of morphine and alcohol dependence, asthma, digestive disorders, and for the relief of depression and fatigue.[19, 27, 43] Freud's associate Carl Kroller demonstrated the powerful local anesthetic properties of cocaine in 1884. In the same year William Halsted, an American surgeon, discovered its nerve-blocking effects. Cocaine was soon hailed in many circles as a medical wonder drug.

Soon after cocaine was introduced, certain undesirable effects of the isolated and potent material began to appear. Dependence problems were frequently reported, even among the medical pioneers in the area, including Halsted.[8, 43] However, little difficulty seemed to stem from the use of natural coca leaf or such products as coca tea and wine.

One of the more famous cocaine users was the fictitious prototype of detectives, Sherlock Holmes. In later books, Holmes gave up his use of cocaine and switched to the tobacco pipe.[43]

In the United States, one of the most popular 'soft' drinks of all time, Coca-Cola®, was developed in 1888 using extracts of coca leaf (containing cocaine) and Kola nut (containing caffeine). Originally, Coca-Cola® was sold as a home remedy rather than a recreational drink. By 1906, when coca came under strict control in the United States, the natural cocaine had been removed from the drink. Large quantities of 'decocainized' coca extract are still used for flavouring purposes in the preparation of Coca-Cola®.[28, 51]

Cocaine has mixed effects, but is generally considered a stimulant and is, in many respects, pharmacologically similar to the amphetamines.[4, 26] The patterns and problems of chronic cocaine use, which began to appear soon after the drug was introduced, bear a marked resemblance to the more recently evolved conditions of amphetamine dependence. Although cocaine was often used a few decades ago by heroin users and others in some of the big cities in North America, it had, for a number of years, largely disappeared from the drug scene. Cocaine is back, however, and can no longer be considered rare in Canada. The use of cocaine is presently severely restricted by its high price and very limited availability. The drug is usually referred to as 'coke', 'snow', or 'flake', and occasionally as 'C', 'girl', 'fly', 'happy dust', 'lady', or 'rock'.

Cocaine is legally classified with the opiates, as a narcotic, although pharmacologically it has little in common with the opiate narcotics.

Medical Use

The main medical use of cocaine today is as a local anesthetic or pain blocker, particularly in operations involving the eye. This use arises from the fact that low concentrations of cocaine block terminal sensory nerve fibres, and higher concentrations produce anesthesia by direct contact with mucous membranes and the cornea in the eye. Cocaine has also been used to treat asthma and colic, and for symptomatic relief in tuberculosis. The exploratory use of cocaine in the treatment of drug dependence at the turn of the century has been abandoned. Today numerous synthetic cocaine-like compounds have replaced cocaine in most of its former medical applications. For example, procaine (Novocaine®) and lidocaine (Xylocaine®) are widely used medically to block pain in local areas for surgical and dental work, and to reduce the pain from burns, earaches, etc.[49, 55]

Chemical Analysis of Illicit Samples in Canada

Few cocaine samples have been subjected to careful chemical analysis in Canada. No cocaine was found among the 621 'street drug' samples reported in 1970 by Marshman and Gibbins in Toronto.[36] The Commission's national survey of analysis facilities and our own collection of drug samples in 1971–72 provide data on seven items alleged to be cocaine.[40, c] Only four of these samples actually contained the drug. In addition, cocaine was found in four other samples where it had not been specified as such. The Health Protection Branch reported the quantitative analysis of 10 police seizures of cocaine in 1971–72.[22, b] These samples ranged from 0.3%–94.2% cocaine with a median of 53.4%. Procaine and amphetamine are sometimes distributed as cocaine or are used to dilute it. Various sugars are reportedly also common diluents.

Administration, Absorption, Distribution and Physiological Fate

Cocaine is a white crystalline powder. In medical practice today, cocaine is rarely applied internally or injected, but is usually administered topically. Epinephrine (adrenalin) is present in official medical preparations of cocaine. In non-medical usage in North America, cocaine is generally sniffed or, less commonly, injected intravenously. The Indians of Peru mix the raw coca leaf with a small amount of lime or vegetable ashes which aid in the extraction of the active alkaloid when the leaf is chewed.

The local vasoconstriction caused by the administration of cocaine limits the rate of its absorption. Nevertheless, cocaine is rapidly absorbed from all sides of application, including the mucous membranes in the nose and mouth, and in the gastrointestinal tract. However, if cocaine is swallowed much of it becomes ineffective before absorption due to chemical alteration in the stomach. Cocaine can be highly toxic because it is absorbed much faster than

it is excreted. Cocaine is partially excreted unchanged and may be detected in the urine, but most of a given dose is rapidly metabolized in the liver.[16, 41, 49, 52, 55] A rapid and extremely sensitive immunoassay technique has recently been developed for the detection of cocaine metabolites in body fluids and tissues.[33]

Psychological Effects

In addition to eliminating pain in local areas, cocaine has powerful psychological effects. The general similarities between the effects of cocaine and amphetamine are so striking that some authorities have subsumed both drugs under the same general classification.[4, 5, 26] Cocaine is much shorter acting, however, and the main effects of a single dose usually dissipate in less than an hour. In contrast to cocaine, the amphetamines do not have any local analgesic action. Most of the effects of cocaine, which are briefly summarized below, are similar to those of amphetamine described earlier.

Small doses of cocaine and coca leaf have long been reported to provide increased energy, muscle strength and capacity to work; a pleasant psychological lift; an improvement in reaction time and simple mental functions; and relief from the discomforts of hunger, thirst, illness and fatigue.[6, 26, 34, 54] Most of these claims have not been subjected to rigorous scientific investigation, however.[31] As with amphetamines, improvement in function is probably most noticeable when prior performance was low due to fatigue or boredom. There has been little research into the psychological effects of chronic cocaine use. A study in South America suggested slightly poorer intellectual functioning in coca chewers than in non-users, but limitations in the study preclude any simple conclusions.[42, 46]

There is a considerable resemblance between the patterns of chronic intravenous cocaine use and the 'speed freak' picture discussed earlier in this appendix. The initial 'rush' or 'splash' from intravenous cocaine has been reported to be essentially the same as that associated with the use of amphetamine,[32] although in other respects many stimulant users claim that the two drugs are subjectively different. Users become extremely self-confident in their physical and mental capabilities, may report increased self-insight and, like amphetamine users, often claim to experience more intense and pleasurable sexual orgasms while under the influence of the drug. Cocaine is very short-acting and a period of indescribable euphoria may be followed by considerable psychological depression within an hour after administration. Consequently the dose is often repeated at frequent intervals in patterns which may include several cycles per hour. Some users have been reported to consume several grams a day, although the actual doses of pure cocaine employed are not certain.

With repeated administration of large doses, a toxic psychosis can develop which is similar to the amphetamine psychosis previously described. As with 'speed', some chronic intravenous users have described the sensation

of animals or bugs burrowing under the skin. Several cases have been reported of individuals who have injured themselves while attempting to dig out imaginary 'crank bugs'. In a few instances, acute psychotic reactions with hallucinations and severely excited behaviour have occurred after a single injection. Some adverse reactions to topical application have also been noted in medical use. Severe paranoia and violence are not uncommon after long cocaine binges. Many observers attribute the classic popular picture of the 'crazed dope fiend' to the chronic user of cocaine—not the heroin user, as is often assumed.[4, 26, 30]

In part because of its very limited use at the present time, significant adverse psychological reactions to cocaine are rare in Canada. None of the surveys of treatment facilities conducted by or reported to the Commission have specifically noted cocaine problems.[23, 24, 38, 45, 47, 50] The national mental health data collected by Statistics Canada indicated only two psychiatric admissions attributed to cocaine dependence in the country in 1970.[14, 48, [e]] (Poison Control Program Statistics are discussed below.)

Physiological Effects

Cocaine's general CNS arousal or stimulant effects are similar to those produced by the amphetamines. Administration of cocaine causes an increased rate of respiration resulting in a rapid but shallow breathing pattern, raises body temperature and produces a marked widening of the pupils. Drying of the mouth and nasal passages occurs when cocaine is sniffed. With higher doses, tremors and convulsive movements result from cocaine's effects on motor systems in the brain and spinal cord. Small doses of cocaine cause a slowing of heart rate, but higher doses result in acceleration. The vasoconstrictive properties of the drug produce an initial rise in blood pressure, but this later reserves and pressure drops to subnormal levels. As noted earlier, cocaine blocks nerve transmission in local application.[4, 37, 49, 55]

As a result of its powerful blood vessel constricting effects, cocaine can damage tissues locally if injected, sometimes leaving small 'pock marks' at the site of injection. Long-term chronic sniffing of large amounts of cocaine can likewise destroy tissue in the nose. Holes in the nasal septum have been reported in some heavy users. Intravenous use of cocaine commonly involves the same problems of unsterile and shared syringes, contaminated drugs, etc., that cause difficulties in the injection of 'speed' and heroin.

There is little evidence of a significant incidence of adverse physiological reactions to cocaine in Canada. We have found no evidence of cocaine deaths in Canada in either our survey of provincial coroner's records or in the reports of Statistics Canada for 1969–71.[11, 12, 13, 39] The Federal Poison Control Program has records of one cocaine adverse reaction in 1970 and six for 1971. None were recorded in 1969. No fatal cocaine poisonings were reported.[10, 44, [f]]

Tolerance and Dependence

In contrast to the amphetamines, it appears that significant tolerance does not develop to most of the effects of cocaine.[4, 18, 31, 34, 53] In fact, increased sensitivity or 'reverse tolerance' with repeated use has been noted by some authors. It has been reported that individuals have self-administered several grams of cocaine in a single day, but that after a period of withdrawal they were still capable of accepting the same amount of drug without ill effects. Although chronic users often increase the frequency of administration and may take the drug several times an hour, there is little general tendency to increase the individual dose to obtain a 'high'.

There seems little question that cocaine can produce, in some individuals, psychological dependence in the sense that there is often a preoccupation with obtaining the drug, compulsive and repeated self-administration, and craving for the drug upon withdrawal in heavy users. The question of physical dependence is less clear. Most authorities feel that no significant physical dependence develops with cocaine use.[4, 18] But here again the picture is quite similar to that of chronic 'speed' use. There does appear to be a disruptive syndrome which occurs upon the withdrawal of cocaine, characterized by overeating, prolonged sleep, and emotional depression. It has been suggested that this syndrome cannot be completely accounted for by the appetite suppression and sleep deprivation that occurs during the intake phase of cocaine use.[26] Thus cocaine, like the amphetamines, may be capable of producing some subtle kind of physical dependence, albeit in a form different from that produced by the sedatives and opiate narcotics.

Cocaine and Other Drugs

In spite of the similarity in effects of cocaine and amphetamine, there have been no reports of cross-tolerance between the two. Some of the effects of cocaine are blocked by reserpine, a major tranquilizer.[56] Some intravenous heroin users have been known to administer a mixture of cocaine and opiates, known as a 'speed ball'. An alternating pattern between the use of cocaine and opiate narcotics, similar to that noted earlier in the section on amphetamines, has also been described. The occasional sniffing of cocaine by users of marijuana and other psychedelic drugs has been reported, and cocaine and cannabis are sometimes used together. (See also Appendix C *Extent and Patterns of Drug Use.*)

A.5 HALLUCINOGENS

Introduction

One of the most remarkable and controversial drugs known today is *d*-lysergic acid diethylamide-25, also called lysergide, but better known as LSD or simply 'acid'. LSD is capable of producing profound and unusual psychological changes in almost infinitesimal doses, with relatively little other

pharmacological effect. Along with related drugs it has exerted significant influence in a variety of aesthetic, scientific, philosophic, religious and social areas over the past two decades. LSD is often considered the prototype of the drug class we have called *Psychedelic-Hallucinogens* (or simply *hallucinogens*), which includes a great number of synthetic and naturally occurring substances with somewhat similar psychopharmacological properties. To date, several thousand articles on LSD and related drugs have been published.

LSD was developed in 1938 by Hofmann and Stoll, in Switzerland, as part of a research program investigating potential therapeutic uses of certain ergot compounds.[129] LSD is a semi-synthetic derivative of lysergic acid, an ergot alkaloid produced by a parasitic fungus, or 'rust', sometimes found on rye or other grains. Closely related substances are also produced in the seeds of certain varieties of tropical morning glory. Most ergot alkaloids are not particularly psychoactive, although some may have a variety of powerful, and often toxic, physiological actions, and have been used for centuries for medical purposes.

Since LSD appeared to be relatively uninteresting in early animal physiological studies, it received little attention until Hofmann unwittingly ingested a minute quantity some years after its original synthesis.[130] He subsequently described his experience as follows:

> In the afternoon of 16 April 1943, when I was working on this problem, I was seized by a peculiar sensation of vertigo and restlessness. Objects, as well as the shape of my associates in the laboratory, appeared to undergo optical changes. I was unable to concentrate on my work. In a dreamlike state I left for home, where an irresistible urge to lie down overcame me. I drew the curtains and immediately fell into a peculiar state similar to drunkenness, characterized by an exaggerated imagination. With my eyes closed, fantastic pictures of extraordinary plasticity and intensive colour seemed to surge towards me. After two hours this state gradually wore off.

To confirm his suspicion that LSD was responsible for this effect, Hofmann investigated further:

> However, I decided to get to the root of the matter by taking a definite quantity of the compound in question. Being a cautious man, I started my experiment by taking 0.25 mg of d-lysergic acid diethylamide tartrate, thinking that such an extremely small dose would surely be harmless, and bearing in mind that the natural ergot alkaloids produce toxic symptoms in man only with doses exceeding several milligrams. After 40 minutes I noted the following symptoms in my laboratory journal: slight giddiness, restlessness, difficulty in concentration, visual disturbances, laughing.

And later:

> I lost all count of time. I noticed with dismay that my environment was undergoing progressive changes. My visual field wavered and everything appeared deformed as in a faulty mirror. Space and time became more and more disorganized and I was overcome by a fear that I was going out of my mind. The worst part of it being that I was clearly aware of my con-

> dition. My power of observation was unimpaired.... Occasionally I felt as if I were out of my body. I thought I had died. My ego seemed suspended somewhere in space, from where I saw my dead body lying on the sofa .... It was particularly striking how acoustic perceptions, such as the noise of water gushing from a tap or the spoken word, were transformed into optical illusions. I then fell asleep and awakened the next morning somewhat tired but otherwise feeling perfectly well....[130]

Since various aspects of the LSD experience were later thought to resemble symptoms of naturally occurring schizophrenia, many investigators became interested in using LSD as a tool for producing an artificial or 'model psychosis' in the laboratory. The possibility of gaining insight into psychiatric disorders by the study of the LSD-induced state stimulated considerable activity in medical and scientific communities and the terms *psychotomimetic* (psychosis mimicking) and *psychotogenic* (psychosis producing) were coined. The subsequent discovery that the LSD experience is, in fact, generally different from natural psychoses has lessened interest in this aspect of its use. The descriptive label *hallucinogenic* (hallucination producing) has gained wide acceptance, although there is some controversy regarding the importance or frequency of hallucinations in the LSD experience. The term *illusinogenic* (illusion producing) is probably more appropriate.

In the 1950s, the exploration of LSD as an aid to psychotherapy began. Much of the early investigation of the use of LSD in the treatment of alcoholics was conducted in Canada under the direction of Abraham Hoffer at the University of Saskatchewan. In 1957, after reviewing the various descriptive names given LSD and related drugs, Humphrey Osmond, then Superintendent of the Saskatchewan Hospital, suggested the terms *psycholytic* (mind releasing) or *psychedelic* (mind manifesting) as more appropriate general labels.[228] For various reasons the latter has gained worldwide usage, although its common application has strayed considerably from its original context, and the word psychedelic may now denote general styles of art, fashion and music which are, in some sense, felt to reflect, enhance, or substitute for the psychedelic drug experience.

In this report, the labels "psychedelic", "hallucinogen" or "psychedelic-hallucinogen" are used interchangeably to refer generally to LSD and LSD-like drugs and, for practical purposes, are considered synonymous.

Non-medical interest in LSD, psilocybin and mescaline began to grow during the 1950s, although such use was apparently largely restricted to a few professional, academic, and artistic experimenters. The drug gained continental notoriety in the early 1960s as a result of experimentation by two Harvard University psychology professors, Richard Alpert and Timothy Leary, who invited other 'explorers' to "Turn on, tune in, and drop out" of the existing social institutions. Their unorthodox religious orientation to the LSD experience is presented in *The Psychedelic Experience,* (a 'trip' manual based on *The Tibetan Book of the Dead*), which became one of the 'bibles' of the psychedelic drug movement.[177, 180] Another significant influence, with

considerably less religious orientation, was writer Ken Kesey's group, the adventures of which are well documented in *The Electric Kool-Aid Acid Test.*[325]

Since 1963, the Canadian Government has controlled the medical and scientific use of LSD, and in 1969 the possession of LSD without governmental authorization was made a criminal offence. Regulation of the legal supply of LSD has apparently had little effect on 'street' use, however, since essentially all of the drug illicitly used has come from clandestine laboratories. Since LSD is odourless, colourless and tasteless in solution and active in almost invisible quantities, effective legal control of its transportation, distribution and use has been extremely difficult. (See also Appendix B *Legal and Illegal Sources and Distribution of Drugs.*)

MDA (methylenedioxyamphetamine) and STP (DOM, dimethoxymethylamphetamine) are synthetic drugs, intermediate in structure between mescaline and amphetamine with some pharmacological properties of each. Closely related compounds which are rarely found on the illicit market include MMDA, TMA and DOET. Relatively little information is available regarding the non-medical use of these drugs and the effects produced by such use.

MDA was originally explored medically for its amphetamine-like properties, and has been shown to have some anti-depressant and appetite-suppressing effects, but it is currently legally available only for experimental purposes. MDA is in some respects similar to, but more potent than mescaline.[100, 113, 266] The non-medical use of MDA has increased considerably in Canada during the past few years.

STP first appeared on the illicit market in California in 1967, where it was heralded as a "megahallucinogen"—a drug "one hundred times as potent as LSD", which was capable of producing an hallucinogenic 'trip' lasting for several days. The label STP is presumably a satirical reference to a commercial automobile engine oil additive (Scientifically Treated Petroleum). Later the words "serenity, tranquility and peace" were appended to the initials. The chemical identity of STP was uncertain for some time and it is likely that the label has been applied to several different drugs and drug mixtures in the past. A number of illicit samples were finally identified as DOM, an experimental compound originally developed by the Dow Chemical Company of California. Since then the letters STP have generally been taken to refer to DOM. In this report STP and DOM are considered synonymous. In spite of the "megahallucinogen" reputation, DOM is considerably less potent than LSD, and 'trips' of long duration are only achieved with unusually large doses.[214, 235, 281]

Phencyclidine or PCP (Sernyl®, Sernylan®) is sometimes called 'the peace pill', 'angel dust' or 'hog'. It was developed in the late 1950s for use as a sedative, general anesthetic and analgesic. After considerable clinical testing its use in humans was discontinued, in part because it often produces agitation and psychotomimetic effects at moderate to high doses. Phencyclidine is still marketed for veterinary purposes, and is the 'animal tranquilizer'

often noted in mass media reports of illicit drug use. It has some subjective effects in common with LSD, but PCP is typically much more sedating, and produces a different pattern of physiological response. Some investigators feel that PCP is pharmacologically more similar to the general anesthetics or volatile solvents than to LSD. The use of PCP in Canada has become significant in the last few years. There is a significant body of clinical data on PCP, but relatively little scientific information exists regarding its non-medical use and associated consequences.[78, 79, 234]

While LSD has had a rather short, and somewhat stormy history, numerous naturally occurring substances with apparently similar psychological effects have been used in the Western Hemisphere for centuries. Perhaps the most widely known are mescaline, from the peyote cactus (*Lophophora Williamsii*) and psilocybin (and psilocin), the active principles in certain 'sacred mushrooms' (teonanactl or *Psilocybe mexicana*). The subjective effects of LSD, mescaline and psilocybin are almost indistinguishable, except that psilocybin has a much shorter duration of action.[4, 140, 324] Other related plant materials include the Mexican morning-glory *ololiuqui* (*Rivea Corymbosa*), and DMT (dimethyltryptamine) which is found in special snuffs used for centuries by certain South American Indians. Harmine and harmaline occur in the *caapi* plant, which is used in the form of a drink by Amazonian natives. Some of these botanical substances were considered divine by the ancient Aztecs and played an important role in religious ceremonies long before the Spanish invaded the land. In spite of the Conquistadors' attempts to destroy the culture and its historical and religious underpinnings, the sacramental use of peyote, for example, spread to the Mexican Indians and, later, in the 19th century to certain North American tribes. Today, peyote is used in religious ceremonies by the Native American Church which has over 200,000 Indian members from 82 tribes in Canada and the United States.[3, 64, 172, 186, 261]

The ritual use of hallucinogenic substances by a contemporary Yaqui Indian sorcerer or 'man of knowledge' in Southwest United States has recently been documented in detail by an anthropologist, Carlos Castaneda, in three monographs.[53, 54, 55] These books record the events which took place during Castaneda's period of apprenticeship to Don Juan, and describe his experiences with peyote, Jimson Weed (*Datura stramonium*) and psilocybin mushrooms.

The *Amanita muscaria* or fly agaric mushroom grows wild in many areas of the world. Its use for psychotropic purposes is best documented, in recent times, in parts of Siberia. Gordon Wasson has conducted a remarkable investigation of *Amanita muscaria* and has proposed that it is the divine soma described in the earliest Hindu literature some 3,000 years ago.[318] Recently, in *The Sacred Mushroom and the Cross,* John Allegro presented the thesis that this mushroom played a significant role in early Christianity.[11] Although *Amanita muscaria* and several varieties of psilocybin mushrooms grow untended in many areas of Canada, it would appear that these mushrooms have been ingested by only a few exceptional experimenters in this country. There is no evidence that the native Indians of Canada have used these mushrooms.

The common spice nutmeg (and mace) has had a long history of medical and non-medical use as a drug which parallels in many respects that of cannabis. The effects of nutmeg and cannabis are remarkably similar, although the nutmeg 'trip' is considerably longer in duration. The nutmeg tree (*Myristica fragrans*) is cultivated in many tropical areas of the world. The active principles of nutmeg are structurally very similar to amphetamine, mescaline and MDA. The use of nutmeg for its psychotropic properties has often been noted in certain groups in North America, but such use has apparently never been extensive.[97, 266, 302, 319]

Certain belladonna alkaloids, such as scopolamine, and other anticholinergic drugs which produce sedation in low doses, but hallucinogenic effects with larger quantities are discussed below in A.8 *Minor Tranquilizers and Non-Barbiturate Sedative-Hypnotics*. There is also some discussion of drugs with certain hallucinogenic properties in A.9 *Volatile Substances: Solvents and Gases*.

Until relatively recently, psychedelic drugs received little general public attention, even though some had been intensively explored over the past century by various writers, scientists and adventurers. Based on his mescaline experimentation, Aldous Huxley presented, in his twin volumes *The Doors of Perception* and *Heaven and Hell*, one of the most lucid and perceptive analyses of some of the possible personal, philosophical and social implications of the psychedelic experience.[138]

The pharmacological classification of cannabis is the subject of much controversy. Cannabis has certain characteristics in common with a wide variety of drugs; under various conditions and doses it has been shown to have stimulant, sedative, analgesic and psychedelic properties. Many investigators feel that cannabis should have a separate and unique category. As it is most commonly used in North America, cannabis in low doses resembles alcohol in some subjective effects. Larger doses are more psychedelic, and with very high doses certain LSD-like experiences are reported. It is clear that any attempt to completely specify a pharmacological classification for cannabis must include a clear delineation of dose, as well as the set and setting of use. The Commission has classified cannabis with the psychedelic-hallucinogen drugs. Since cannabis has already been dealt with in great detail in a separate final report, little further reference will be made to cannabinoid drugs in the present discussion.[47]

LSD is the best studied and most frequently encountered psychedelic-hallucinogen in Canada (excluding cannabis), although in recent years, significant quantities of PCP and MDA have been identified. STP is only occasionally found. The use of other LSD-like drugs appears to be rare in this country. Although one frequently hears fascinating stories of exotic drugs created by 'hippie chemists', there is no evidence that such compounds are used significantly. The general discussion which follows focusses primarily on LSD, with references to other related drugs, including PCP, MDA, mescaline, and psilocybin, where distinctions are appropriate and data are available.

Medical Use

There is currently no widely accepted medical use of LSD, although it may be employed experimentally for therapeutic purposes. There have been numerous impressive reports of LSD successes in the treatment and rehabilitation of alcoholics, opiate narcotic dependents, criminals and various psychiatric patients.[105, 126, 178, 257] LSD has also been used with patients dying of cancer, to alleviate their anxiety and pain, and to help them adjust to the prospects of death.[157, 230] Many of these leads have not been followed up with adequate scientific investigation, however, and several recent controlled studies have not substantiated the claim that LSD adds to the effectiveness of conventional psychotherapy.[75, 171,196, 272]

Two basic forms of psychological treatment with LSD have developed: *psycholytic* therapy, which uses small or moderate doses on repeated occasions, sometimes over a period of several months; and *psychedelic* therapy which calls for higher doses and a more profound acute effect and is, as a rule, given only once or twice. While some investigators claim that LSD, itself, is more effective than psychotherapy, others claim that its usefulness is mainly limited to the removal of therapeutic 'blocks' which may occur at times in the course of psychotherapy. Still others feel that LSD has no useful contribution to make to psychiatric treatment. Most clinicians who have had experience with this form of therapy stress the need for a careful selection of patients and for special qualities and experience in the therapist.

More sophisticated scientific investigations of possible therapeutic uses of LSD are underway and may help clarify some of these issues. It seems justified to say at this time, however, that the general medical effectiveness of LSD has not been adequately demonstrated.

Phencyclidine (PCP) is no longer employed as a sedative-anesthetic in humans, although it is available for veterinary purposes. Various forms of MDA (e.g., MER-22, SK&F 5 and SK&F L-5) have been evaluated in the treatment of schizophrenia and depression, and were investigated for their anorectic (appetite-suppressing) effects. MDA is not used medically at the present time, however.[24, 78, 79, 80, 100, 113, 134, 222]

Chemical Analysis of Illicit Samples in Canada

Illicit drug samples submitted to authorized laboratories for identification are often those suspected of being adulterated, some other drug than it was alleged to be, or the cause of adverse or unusual reaction. Even though such samples cannot be considered representative of the available illicit drugs, some useful general information can be obtained from an examination of the data from these laboratories. The Commission's national survey of drug analysis facilities in Canada during 1971–72 and our own collection of illicit samples provide considerable data on LSD and related drugs.[218,[c]] These two sources of data are considered together in the following summary.

Of 162 samples alleged to be primarily LSD:

69% were LSD alone
9% contained LSD and other drug(s)
9% were other drug(s)
5% were primarily products of faulty or incomplete LSD synthesis
8% contained no drug

Of ten samples presented specifically as LSD mixtures, only one was the alleged combination, and the remainder contained LSD only. In addition, LSD was frequently found in samples represented as other drugs. A total of 45 LSD-PCP combinations were found, only one of which was presented to the analyst as such. Seven samples of LSD-barbiturate mixtures were reported, but no other specific LSD combination occurred more than a few times each in these data. A total of 208 relatively pure LSD samples were found, and of 183 for which some alleged identity had been specified, 111 (61%) had been presented as LSD.

Of 64 samples alleged to be primarily MDA:

42% were MDA alone
20% were MDA and other drug(s)
27% were other drug(s)
11% contained no drug

Of 12 samples presented specifically as MDA mixtures, none had the alleged composition and seven contained only MDA. A total of 52 samples of unadulterated MDA was found, and of the 42 for which an alleged identity had been specified, 27 (66%) had been presented as MDA. MDA combinations included LSD, PCP or amphetamines. No evidence of faulty synthesis of MDA was noted in these data. Two samples of MMDA and 17 STP (DOM) samples were reported. All of the STP-containing samples had been presented as some other drug.

Forty-seven samples of PCP alone were found, as well as 57 PCP combinations (45 with LSD and 9 with methamphetamine). No indications of faulty or incomplete PCP synthesis were noted. In spite of the fact that PCP was detected in a total of 104 samples, there were only two cases which were presented as PCP or PCP mixtures. In every other instance the drug was either alleged to be something else or its identity was not specified. Eighteen of 26 alleged tetrahydrocannabinol (THC) samples were actually PCP, and none contained THC.

There were 171 samples alleged to be mescaline, but only five (3%) contained any trace of that drug. One hundred and thirty-five (79%) were other drug(s) and 31 (18%) contained no drug. The samples erroneously presented as mescaline included 43 LSD, 33 LSD and PCP, 18 PCP, 11 STP, 9 methamphetamine, and a variety of other drugs.

Thirty-two samples were alleged to be psilocybin. This drug was tentatively identified in only one case. Twenty (63%) of the samples were other drug(s) and 11 (34%) contained no drug. Fifteen of the samples were actually LSD.

In an earlier study, Marshman and Gibbins of the Addiction Research Foundation reported on the composition of 621 illicit drug samples collected and analysed in Ontario between January 1969 and February 1970.[201] The data reported is generally similar to that presented above. Of 176 alleged LSD samples, 56% were relatively pure LSD. None of 58 alleged mescaline samples contained any of that drug (about half were LSD). The analysts were unable to detect the presence of a second drug in any of 46 samples which had been presented as combinations. There were 29 samples of MDA submitted for analysis, of which 62% had been presented as that drug. Only a few PCP samples and PCP-LSD mixtures were identified at that time.

The Federal Health Protection Branch (HPB) has informed the Commission of the quantitative analysis of several hundred hallucinogen samples selected from among those seized by the police during June 1971–October 1972.[114,[b]] Many of these samples had been chosen for this special analysis because of previously detected impurities and, consequently, they cannot be considered representative of either the drugs on the street or of police seizures in general. Of 229 samples containing LSD, 166 (73%) contained no impurities or other drugs, 34 were LSD-PCP mixtures, and 16 contained LSD and methaqualone. No other mixture occurred more than a few times. Products of faulty or incomplete LSD synthesis were sometimes noted. Because of the frequency of LSD-PCP mixtures in police seizures, HPB officials considered this combination as a separate category rather than as an incidence of adulteration. Excluding the LSD-PCP mixtures, the 117 unit doses of LSD-containing samples analysed ranged from a mere trace of LSD up to 305 mcg of pure LSD, with a median of 141 mcg. Only 8 of 73 PCP-containing samples did not include another drug in combination. These eight PCP samples contained between 1.7 and 49.0 mg PCP each with a mean of 10.9 mg. Median quantitative values for 26 unit doses of LSD-PCP mixtures were 41 mcg of LSD and 1.8 mg of PCP. There were also 10 PCP-ephedrine mixtures, in which a mean of 4 mg PCP was present. No products of faulty or incomplete synthesis of PCP were noted.

Of 126 seizures of MDA analysed by HPB in this series, only 7 contained other drugs (heroin, methamphetamine or PCP). Sixty-one unit dose samples ranged from 0.6 to 107 mg pure MDA, with a median of 37.5 mg. The 57 samples found in powder or bulk form were between 0.1% and 91.3% pure MDA, with a median of 36.6%. Fifteen seizures of LBJ (methylpiperidylbenzilate) were analysed, of which only three did not include other drugs. These samples typically contained a little over one milligram of LBJ per unit dose. By-products of synthesis were found in 11 cases.

A *The Drugs and Their Effects*

Overview

Subject to the sampling restrictions noted, the data available on the analysis of illicit drugs allows some tentative conclusions regarding the hallucinogenic drugs used non-medically in Canada. Excluding cannabis, LSD is the most frequently encountered of these drugs. For example, LSD alone or in combination with other drugs was detected in 292 (66%) of the 445 hallucinogen (non-cannabis) samples in the Commission study. PCP was found in 104 (23%) and MDA was identified in 72 (16%) of these samples. (Note that because of drug mixtures, these categories are not mutually exclusive.) In total, LSD, PCP, MDA, or combinations involving these drugs made up 94% of such samples. Data from the Addiction Research Foundation and the Health Protection Branch provide generally similar pictures. STP and LBJ have been identified on only a few occasions. Other LSD-like drugs, including mescaline and psilocybin, have rarely been documented in Canada. The Commission's data is particularly significant in this regard since special effort was made to obtain information on rare or unusual drugs or combinations, yet on analysis, samples of such substances were almost invariably found to contain only common drugs. It is obvious from the data that misrepresentation often occurs in the illicit market and that the LSD and related drugs available are highly variable in both purity of the material and the quantity contained in a unit dose. The user has little objective basis for assessing the identity, quality or dose of such drugs prior to use.

Drug combinations are not uncommon, but with the exception of PCP, most samples contain only a single active compound. The present studies are biased in favour of collecting and identifying mixtures and unusual drugs and consequently exaggerate the frequency of their occurrence in the general illicit market. While a few unusual combinations of several different substances have been identified, the vast majority of mixtures are made up of only two common drugs. Samples which are represented as mixtures on the illicit market are rarely as alleged and typically contain only one active substance.

In Manitoba, a poisoning was attributed to an overdose of the stimulant strychnine, which had reportedly been sold as MDA.[217] In all of the data reviewed here, strychnine was not found in any of the combinations where it was alleged to occur, but was reported in 4 other instances. Strychnine was not found in any of 2,000 police seizure drug samples analysed by the HPB in 1971,[114] nor has it ever been identified in the analyses conducted at the Addiction Research Foundation of Ontario.

It would appear that most of the LSD available on the illicit market is of reasonable quality, although evidence of crude manufacture is present in some samples. Available data suggest that 140 mcg is a typical unit dose in Canada. Concern has been expressed regarding the possible toxic properties of ergot alkaloids present in a few samples as a result of faulty or incomplete LSD synthesis. Since there has been no direct testing of the biological activity

of such samples, firm conclusions can not be drawn. Serious toxicity would seem unlikely at typical LSD doses because of the small quantities of ergot compounds generally involved, although unusually large doses of poorly synthesized LSD may involve some risk.

It would appear that PCP is rarely identified as such on the illicit market, but instead is sold alone or in mixtures, primarily represented as mescaline, THC or, less commonly, other rare drugs. Consequently, epidemiological data involving self reports by users, as well as clinical data of adverse reaction or poisoning, are likely to grossly underestimate the involvement of PCP. Chemical identification of the drugs used in such reports is almost non-existent at the present time. Any PCP cases are likely to be erroneously attributed to other drugs. Reports involving the illicit use of mescaline or psilocybin are likely to actually represent LSD and/or PCP cases.

There has been some concern in the literature that the illicit production of PCP carries a special risk of 'missynthesis', the by-products of which may be highly toxic.[237] Although the original source of the illicit PCP is uncertain, no evidence of products of faulty or incomplete synthesis of this drug has been found in Canada.

It is interesting that PCP is the only drug in these data which occurs less often alone than in combination with other drugs (primarily with LSD). This is especially significant for the discussion of drug effects which follows, since there is virtually no experimental information available on PCP-LSD interaction in humans.

Administration, Absorption, Distribution and Physiological Fate

LSD and most related drugs are usually taken orally, but may be sniffed in powdered form or injected in solution. Some can be effectively smoked. While LSD is available in ordinary capsules or tablets, it is often impregnated in such innocuous substances as sugar cubes, candies, biscuits, and cloth or blotter sections for oral use. LSD is well absorbed from the gastrointestinal tract, is distributed rapidly in the blood and easily diffuses into all tissues including the brain, and in pregnant females crosses the placental barrier into the fetus. LSD does not have any particular affinity for neural tissues and approximately one per cent actually reaches the central nervous system. Essentially all of the LSD in the body is metabolized in the liver and excreted in the urine in the form of inactive compounds. Likewise, MDA and PCP are primarily excreted in the urine in the form of metabolites.[9, 64, 78, 79, 234, 281]

Recently developed radioimmunoassay techniques allow the rapid detection of minute quantities of LSD in body fluids and tissues.[71, 312] PCP, MDA, STP, mescaline and psilocybin can be detected in body fluids and tissues by standard analytic methods.[19, 57, 58, 156, 288, 294]

Psychological Effects

LSD is one of the most potent biologically active substances known and can exert noticeable psychological effect with 20–30 mcg (millionths of a gram)—an almost invisible quantity of pure LSD. Taken orally, LSD effects typically occur within an hour and peak at 2 to 3 hours, but may be much faster; response to intramuscular injection usually appears within ten minutes; and if the intravenous route is used, the latency may be only a few minutes or less. Intraspinal injection produces an almost instantaneous effect. The duration of the action depends to a certain extent on the amount taken, and with typical doses, major effects usually last 6–10 hours with gradual recovery over a similar period. Peak effects correspond with blood levels of LSD.[9,64]

Depending on dose, the duration of major effects of mescaline, MDA, STP and PCP may be comparable to those of LSD. The main effects of psilocybin dissipate very rapidly, and usually last only a few hours, and DMT is even shorter acting. The following figures represent typical oral doses of these various drugs as noted in the scientific literature, but cannot be taken as precise quantitative equivalents.[4,78,127,140,244,265,324]

LSD	0.1–0.2 mg (thousandths of a gram)
Psilocybin	5–10 mg
STP (DOM)	5–10 mg
PCP	5–10 mg
MDA	75–150 mg
Mescaline	250–500 mg

The psychological effects of LSD and related drugs are not readily predictable, and are determined to a considerable degree by various personality factors in the individual; his past history and experiences; his attitudes, expectations, and motivations; the general setting in which the drug is taken; persons accompanying the 'trip'; and external events occurring during the experience. While the psychological response to LSD is to some extent dose-related, certain effects appear to be relatively independent of dose over a considerable range. Increased quantities often seem to affect the duration more than the intensity or quality of the 'trip', although with very high doses confusion and disorientation are more likely to occur.[6, 61, 98, 127, 141, 239]

Subjective psychological effects of LSD and LSD-like drugs are extremely difficult to describe and many scientists are quite pessimistic about the possibility of presenting an objective list of responses which in any way communicates the essence of the experience. The intensely personal nature of the effects further limits description and generalization. Pahnke and Richards[232] have described several major types of psychological experience which have been reported with psychedelic drugs. The outline presented below is based on that proposed by these researchers. While the list is certainly not exhaustive and does not describe necessarily discrete or non-overlapping

categories, it provides a convenient basis for the discussion of LSD-like effects. It should be noted that not all of the experiences listed happen in all sessions or in all individuals, although several may occur in varying degrees, in sequence or simultaneously, during a 'trip'. The relative frequency of these various experiences is not indicated by the order in which they are presented here.

First is the *psychotic adverse reaction,* or 'freak-out' which may be characterized by an intense negative experience of fear or 'nightmarish' terror to the point of panic, complete loss of emotional control, paranoid delusions, hallucinations, catatonic features, and, perhaps, profound depression and sense of meaninglessness. Such states are usually of short duration, although prolonged reactions have been noted.

Second is the *non-psychotic adverse reaction* in which the person may experience varying degrees of tension, anxiety and fear, unpleasant illusions, depression and despair. Inappropriate or disordered social behaviour may occur. This kind of reaction may differ from the first in the intensity of the experience and in the degree of control and 'reality contact' expressed by the individual. Such unpleasant experiences are commonly labelled 'bad trips' or 'bummers'.

Third is the *psychodynamic psychedelic experience* characterized by a dramatic emergence into consciousness of material which had previously been unconscious or suppressed. Strong emotional feelings can accompany what may be experienced subjectively as a reliving of incidents from the past or a symbolic portrayal of important conflicts. Such effects are often sought in LSD psychotherapy.

Fourth is the *cognitive psychedelic experience* characterized by an impression of astonishingly lucid thought. Problems may be seen from a novel perspective, and the interrelationships of many levels of meaning and dimensions may be sensed simultaneously. The relationship between this experience and naturally occurring insight and creativity has been the subject of considerable interest and speculation.

Fifth is the *aesthetic psychedelic experience* characterized by a change and intensification of all sensory impressions, with vision often most affected. Fascinating alteration in sensation and perception may occur; *synesthesia* or crossing-over of sensory modalities may be produced (music and other sounds may be "seen", for example); objects such as flowers or stones may appear to pulsate or "become alive"; ordinary things may seem imbued with great beauty; music may take on an incredible emotional power; and visions of beautiful colours, intricate geometric patterns, architectural forms, landscapes and "almost anything imaginable" may occur.

The sixth type of psychedelic experience has been called by such names as *psychedelic-peak, cosmic, transcendental,* or *mystical.* Some of the psychological phenomena which are said to characterize this experience, are: a sense of unity or "cosmic oneness" with the universe; a feeling of transcendence of time and space; a deeply felt positive mood of joy, blessedness,

love, and peace; a sense of sacredness, awe and wonder; a feeling of profound theological or religious awareness; a feeling of insight into reality at an intuitive, non-rational level; an awareness of things which seem logically contradictory and paradoxical; and a belief that the experience is beyond words, non-verbal and impossible to describe. The full peak experience, in its entirety, does not occur in the majority of individuals, is usually transient, and does not last for long in its full intensity, although it may have persisting effects on attitudes and behaviour.

With few exceptions, little general information can be given as to the relative frequency of occurrences of these various types of psychedelic drug reaction since the response is largely determined by such variable factors as the particular individual involved, his set and the setting. As is often the case in science, techniques designed to measure the effects of these drugs may greatly influence or distort the phenomenon under study. Savage has pointed out, that unless the LSD experience takes place

> . . . in a secure setting, with sufficient emotional support where S (the subject) feels safe to encounter the bizarre and often powerful manifestations of his own mind unharassed by tests, interpretations, and the coldly precise scientific analytic attitudes, the only result can be confusion and paranoia.[358]

Reports of "objective study" of LSD's subjective effects vary considerably in content and often appear to be as much a function of the individual scientist's conceptual orientation and experimental method as they are of the subjects and the drug itself. Some researchers report that LSD experiences in their subjects are definitely unpleasant and anxiety-ridden, and that subsequent sessions are uniformly avoided, while other scientists claim that anxiety is infrequent and that subjects generally enjoy the sessions and are eager to participate further.[122, 269, 304] Experiences in non-supervised and indiscriminate settings are undoubtedly even more variable.

It is generally reported that LSD has deleterious effects on performance on tests requiring a high degree of attention, concentration or motivation. It is often difficult to get meaningful data from such measurements, since subjects frequently become engrossed in the subjective aspects of the drug experience and lose interest in the tasks presented by the investigators. Psychological tests are often seen as absurd or irrelevant by the subjects. After the drug, performance on standard tests of intelligence, learning, memory and other cognitive functions, as well as certain psychomotor tasks generally show temporary impairment, sometimes lack of change and, more rarely, some improvement.[67, 127, 131, 150, 170, 247, 276, 322]

In some situations gross impairment of judgment may occur, but this is not common under experimental conditions. Later recall of events occurring during the drug experience is generally good, and amnesia is rare. PCP produces more disorganization of thought and confusion than the other LSD-related drugs. Delirium, agitation and other features of alcohol-like inebriation are commonly reported with high doses of PCP, but not with the other drugs discussed in this section.[78]

Effects on driving skills have not been systematically investigated, although related experimental data, reports by users, and certain eye witness accounts, suggest that driving ability would usually be drastically reduced by the acute effects of LSD. There is no evidence that the drug has been a significant factor in automobile accidents or traffic violations, however.[163, 204, 227, 315] Apparently few LSD users drive while under the influence of the drug. Further research in this area is needed—especially the investigation of persons involved in traffic accidents. Recent advances in the detection of LSD and related drugs in body fluids and tissues enable a more sophisticated approach to such study.[71]

Changes in visual perception usually play an important role in the psychedelic drug experience. Colours often appear clearer, brighter and more vivid, and alterations in the form or size of objects are typically noted. Subjects report that afterimages last longer, and tinges of colours or "halos" may be seen around the edges of certain objects. The sense of visual depth is usually enhanced but may be decreased, perspective is often altered, and stationary objects may seem to undulate and change in contour and shape.[33, 46, 112, 127, 141, 164, 202, 246] Profound changes in visual imagery are among the most characteristic effects of drugs of this class.[67, 138, 169, 186, 267] The stimulation of visual imagery is most pronounced in the dark when the eyes are closed, although the sensations may also occur to lesser degrees when the eyes are open and, more rarely, under normal lighting conditions.[232] Visions of luminescent colours, flashes of light, gem-like objects, intricate geometric and kaleidoscopic patterns, landscapes, and architectural forms are commonly reported. Stimulation of other sensory modalities such as hearing may induce changes in these visual phenomena.[112, 117, 165] Kluver has suggested three general perceptual forms which typically occur: spiral-like; tunnel- or funnel-like; and grating or lattice-type forms.[168] Commission research has confirmed the existence of these visual form constants and other LSD-like visual imagery effects with THC and marijuana.[216, 268] MDA is apparently less likely than the other LSD-like drugs to produce these visual effects.[222]

Some subjects report that LSD enhances certain subjective qualities of other sensory modalities as well. Music may be especially beautiful, and some persons report that the taste of food and drink becomes more vivid, and the sense of smell more acute after the drug. Evidence of objective changes in these areas are limited, however, and many individuals do not experience significant alteration in auditory, gustatory or olfactory perception.[77, 112, 124]

Changes in the perception of one's body and limbs (often called body-image) commonly occur with psychedelic drugs. Subjects regularly report that body parts feel strange or unusual, as if shape, size, weight and various bodily sensations were altered or distorted. Changes in tactile perception are typical and include numbness, increased sensitivity to textures and shapes, and a tingling feeling in the skin. Parts of the body or mind may feel as if detached or floating free. Dreamy, floating sensations are very common, but often come and go in wave-like fashion.[33, 61, 112, 150, 187, 189, 199, 202]

One of the most uniformly cited and significant effects of LSD and related drugs is the alteration of ordinary time perception or time sense. Subjective time is almost invariably faster than objective "clock time" with psychedelic drugs, and subjects typically overestimate the passage of time. Moments may seem like hours, and time may seem to be transcended. Pleasant experiences may extend indefinitely, or, on the other hand, an acute 'bad trip' may seem like an interminable horror. PCP, in contrast to the other drugs discussed here, tends to produce an underestimation of time. Time perception effects may be related to changes in short-term memory or may reflect an alteration in the general speed of an "internal clock" in the brain.[16, 35, 73, 161, 202]

It has been frequently reported that PCP is much more likely than other LSD-like drugs to produce feelings of isolation and apathy in users. The disturbance in sensory input produced by PCP is considered by some investigators to resemble sensory deprivation, and is quite distinct from the general sensory effects of LSD.[78, 194, 212]

There is some controversy regarding the extent to which LSD and related drugs produce hallucinations. This question is primarily a problem of semantics. There are many definitions of the word hallucination, and there is little agreement in scientific circles regarding its specific delineation. Some investigators would subsume under the general label of hallucinations the various alterations in visual perception and other sensory changes described above. Others have suggested that some of these effects might better be called illusions, and still others feel that neither term is appropriate and that these phenomena should be considered, in a broader context, as altered states of consciousness and perceptual awareness. Many investigators restrict the use of the word hallucination to false sensory impressions which are believed to be real by the person experiencing them. In this sense, LSD and related drugs rarely produce hallucinations, since subjects are almost always aware that the perceptual changes are due to the drug and, typically, do not attribute to them significant independent existential reality.[61, 66, 127]

Contentions are often made that LSD can elicit new levels of spontaneity, insight, problem-solving and creativity. These claims are very difficult to assess scientifically, since the effects described are often highly subjective and personal, and are hardly amenable to empirical validation. The problems of studying creativity in the laboratory are considerable, and little is known of the basic psychology of such cognitive processes. A generally agreed upon definition of the concept of creativity has eluded investigators so far, and few meaningful tests are available. Studies of the effects of psychedelic drugs on allegedly creativity-related interests and behaviours have produced inconsistent results.[36, 116, 145, 206, 289, 301, 327] Often performance does not reflect the subjective impressions of the drug experience. Sophisticated scientific investigation in this area is only just beginning, and the question of subtle effects on creative processes in certain individuals must be answered by future research.

Current arguments as to whether LSD is truly 'consciousness expanding' as its proponents contend or 'consciousness constricting' as its opponents assert, will probably not be resolved by science in the near future, since it seems unlikely that such hypotheses can be put to adequate empirical test given the current state of technology.

Most authorities agree that LSD does not have a specific aphrodisiac or sex-drive stimulating effect. Some users indicate an enhanced appreciation of sexual experience, while many others report a total disinterest in sex while on a 'trip'. Some increase in sexual behaviour may occur as a result of a lessening of inhibitions and an increase in emotionality, tactile appreciation, and interpersonal contact. LSD has been used in the treatment of sexual disorders of psychological origin (e.g., frigidity and impotence), although its general usefulness has not been clearly demonstrated in this area.

The possible religious significance of psychedelic drug experiences has been the subject of heated controversy for centuries. While many authorities have pointed out basic similarities between drug-induced feelings of transcendental or mystical awareness and the *satori* or *kensho* of Zen Buddism, the *samadhi* of Hinduism or the *beatific vision* of Christianity, others have been outraged by the suggestion that such 'instant mysticism' could be produced chemically. It is quite apparent, however, that a considerable degree of religiosity pervaded the psychedelic drug movement of the 1960s and has played a major role in the use of such drugs in other cultures. The major theoretical positions and scientific research in this area have been reviewed by several investigators and these reports provide experimental support for the notion that drug-evoked experiences may have religious significance for certain individuals.[11, 202, 279]

Perhaps the most rigorous scientific evidence comes from Pahnke's controlled psilocybin experiment with seminary graduate students, conducted in the setting of a Good Friday religious service.[232] He notes that: "Those subjects who received psilocybin experienced phenomena which were indistinguishable from, if not identical with, the categories defined by our typology of mysticism." The religious aspects of the psychedelic experience apparently depend a great deal on the individual, his values and expectations, and the setting involved, and do not normally occur with great intensity in most persons or in most situations. Masters and Houston report that 6 out of 206 of their subjects attained a mystical experience,[202] while other researchers report no such events and still others, a much higher incidence. Differences in semantic meaning, definition and criteria may account for part of these discrepancies. The "objective validity" of drug-elicited religious experiences, however, is by nature untestable in the scientific sense, and the area will doubtless remain in a storm of controversy.

Adverse Psychological Reactions [J]

As noted in A.1 *Introduction* the term *adverse reaction*, as traditionally applied to the medical use of drugs, refers to significant undesirable or nega-

tive side effects of the drug. The distinction between main or desired effects and the multitude of other side effects which the drug may have is not absolute in any sense, and the application of these terms generally depends on the conditions of drug use. In the medical use of drugs, the desired and undesired effects are relatively easy to define in a specific treatment context, although the labels may change with the aims of the therapy.

In the area of the non-medical use of drugs, defining adverse reactions becomes considerably more complicated. With hallucinogens, for example, personal and social attitudes and norms often dominate in the interpretation of drug effects.[108] What may be a desirable or pleasurable effect to one individual in a certain situation may be considered an adverse response or a side effect in another situation or to another individual. In a survey of physicians regarding adverse reactions to LSD, one respondent stated, "From my understanding of the effects, I would consider *all* reactions to LSD as 'adverse' regardless of the immediate subjective response."[307] Clearly, not all LSD users or other observers share this opinion. As Bialos indicated, in discussing some of the difficulties with defining marijuana adverse reactions:

> . . . drug users, the non-drug user friend, the professional clinical observer, the researcher, the law enforcement official, and the middle-aged, middle-class citizen may all have different criteria for defining the syndrome.[29]

Tart has proposed two criteria for selecting what he believes would be unequivocally negative effects:[298]

(1) the effect is clearly unpleasant to the user;
(2) it has no redeeming value, other than as a possible lesson to the user.

While most observers might agree in principle with the approach, considerable conflict among individuals would undoubtedly arise in the application of these criteria in many practical situations. Even if agreement were reached as to whether a particular drug-associated condition is positive or negative, determining cause and effect relationships can be a formidable task. It is often very difficult to isolate the alleged effects of LSD from the possible influence of cannabis, since LSD users are almost invariably users of marijuana and hashish as well. Other drugs are also involved in many cases where possible chronic effects are a major issue.

In spite of these ambiguities, a number of rather specific concerns have developed regarding possible adverse psychological reactions to hallucinogenic drugs. Some of these alleged effects include acute adverse reactions such as depression, anxiety, panic or psychotic-like, short-term responses; augmentation of pre-existing neuroses, character disorders and adjustment problems; functional psychoses, in which drugs might serve as a precipitating or complicating factor; long-term changes in personality, behaviour or life style associated with chronic use (for example, the so-called "amotivational

syndrome"); specific psychoses or dementia of a chronic nature caused primarily by the drug; and "flashbacks" or recurrences of previous drug effects.

In the past decade there have been numerous clinical reports of adverse psychological reactions to hallucinogen use in North America. The majority of these reports display considerable methodological problems which impose severe limits on their usefulness. Pre-drug personality, cause and effect relationships, and details of both the general patient group and the overall catchment population from which the subjects were drawn are rarely adequately explored and presented. Some well-documented reports have appeared, however, and certain recurring patterns are becoming apparent.

An LSD-induced 'bad trip' is typically a self-limiting reaction of short duration, lasting only a few hours. Although much more prolonged responses sometimes occur it may range from a mildly negative or ambivalent experience to an episode of intense terror and nightmarish panic. Such adverse reactions often seem to focus on the fear of death, fear of permanent insanity, basic sexual conflicts, and fear of legal repercussions in illicit users, or may be precipitated by an objective 'hassle' or problem of real or imagined significance. Under the influence of LSD, it is often difficult to cope with immediate problems which arise, and emotional vulnerability may be increased. 'Bad trips' seem to occur most often when the individual has had little experience with hallucinogenic drugs, is poorly prepared, alone, or in an otherwise unprotected or unsupervised setting. While an experienced 'guide' or therapist can often help prevent or alleviate negative reactions, this is no guarantee against an unpleasant experience. Neither are earlier positive experiences—severe 'bad trips' have been noted in individuals who had previous long histories of unequivocally pleasant psychedelic experiences.

Illicit users of LSD commonly voice the opinion that 'bad trips' are caused by bad drugs and that 'pure acid' is relatively free from adverse reactions. These claims are rarely based on chemical analysis. Although contaminants and other drugs occasionally found in illicit market LSD can undoubtedly affect the experience, it seems unlikely that a large proportion of the negative reactions reported can be accounted for by adulterants. It is well-documented that 'freak-outs' do sometimes occur with pure LSD.

Becker has proposed an explanation for the occurrence of anxiety reactions to hallucinogenic drugs, which is gaining considerable support.[29, 30, 31] Hallucinogenic drugs produce effects which are qualitatively different from those a non-user is likely to expect or have experienced before. In many instances, it is the interpretation or meaning which the user attaches to these radically different experiences which determine the subsequent emotional response. Effects which are considered tolerable or even interesting or pleasurable to experienced users, may be frightening to a novice, who may fear a permanent derangement of his mind. Hallucinogens sometimes produce transient waves of mild anxiety or paranoia, which the regular user usually correctly attributes to the drug and has learned to control. These

same effects may convince the novice that he is insane and bring on a severe panic. The response of others to this fear is of great importance—if they are not alarmed, and reassure him that the effects are not unusual or permanent, the anxiety reaction may be minimized. On the other hand, non-users, including some police and medical personnel, may react with alarm, and reinforce the notion that the person is at least temporarily insane (psychotic), thereby adding to his distress. Becker's hypothesis predicts that as familiarity with the acute effects of hallucinogens in our culture increases, the frequency of short-term panic reactions among users will decrease.

The frequency of suicide among LSD users is not known, but a few cases have been documented. Suicidal thoughts have often been reported, but there is little indication that such notions are carried through. Some data on suicides among persons who have taken LSD in medical settings are discussed later. Attempts at self-mutilation have been reported on rare occasions. Accidental deaths associated with hallucinogen use have been reported and a number of fatalities or serious injuries have been noted as a result of a loss of critical judgment or attentional processes. For example, a few individuals have jumped from buildings or trees apparently under the delusion that they could fly or were indestructible.[63, 127, 259, 272] Stories of persons who had become permanently blind while staring at the sun during LSD trips were generated by a state official in the United States and widely circulated in the public media. These reports were subsequently shown to be a hoax and no such cases are on record.[224]

Fear, panic and aggression may result from a 'freak-out', but homicides associated with LSD use are rare and only a few have been documented.[167, 238] Reports of violence resulting from the use of LSD have generally not been supported,[89] although there may be some significant exceptions. The majority of non-drug arrests associated with LSD use in Canada seem to be on the order of "disturbance of the peace" offences[251, 252] and there is little evidence that LSD plays a significant role in major crimes.

Recurrence of certain aspects of hallucinogen experiences ("flashbacks" or "echos") of varying duration and intensity have been reported over periods ranging from a few months to more than a year after the last (or only) LSD use.[118, 249, 272, 305] The quality of these experiences, which usually last only a few minutes or less, may depend on as many factors as the original effects. They may be triggered or precipitated by drug-associated stimuli which were previously associated with drug experiences, by seemingly irrelevant stimuli or events, by other drugs, or they may appear spontaneously.

According to Keeler and associates the recurrence of a drug-like effect (or "flashback") is not necessarily an adverse reaction and should be classified as such only if it precipitates anxiety or interferes with function.[160] "Spontaneous recurrences are tolerated by some and enjoyed by others." They note that the recurrence of clinical psychopathology that was present during the drug reaction is not a spontaneous recurrence of the drug effect.

Discrete recurrences may be on a continuum with more subtle effects of drug use. For example, some subjects claim that their perceptual awareness was increased by hallucinogen use and that some degree of this enhancement remained with them after use. Perhaps also related is the 'contact high' —the experience reported by some users of feeling somewhat 'high' without the drug when in the presence of others who were 'high'. Although these various post-intoxication responses may be in some respects related psychologically and physiologically, in most situations they cannot be considered the same phenomena. The lack of clear agreement as to essential definitions in these areas prevents simple interpretation of the very limited data available. Definitions of "flashbacks" or "spontaneous recurrences" rarely accompany clinical reports in the literature.

There is little agreement regarding the frequency of these ill-defined recurring phenomena. In a recent survey of metropolitan Toronto high school students, 60% of LSD users reported experiencing "flashbacks" of some kind.[274] Of students who had used the drug 21 times or more in the past six months, almost three-quarters reported such recurring experiences. In contrast, other surveys report that about one-quarter of LSD users have had "flashbacks".[42, 290] Horowitz estimated that approximately 5% of repeated hallucinogen users have experienced "repeated intrusions of frightening images" in spite of volitional efforts to avoid them.[135] Studies of persons who have been given LSD under medically controlled settings have rarely found evidence of significant adverse recurrences.[65, 74, 121, 204] It is likely that these various studies are examining different phenomena and comparisons among them seem rather meaningless. Further research is needed, applying more rigorous definitions.

A number of clinical reports have appeared which suggest that the chronic use of hallucinogens may be causally associated with a variety of psychological problems of a more prolonged nature than the generally accepted acute reactions. Although most negative LSD experiences appear to be of short duration, prolonged psychotic episodes lasting months or even years have reportedly been elicited by LSD. Many investigators contend that such extreme experiences occur only in individuals already predisposed to psychotic reaction, and are simply precipitated by the stress of a 'bad trip'. In most of the cases described, considerable prior psychopathology existed, although this is reportedly not always the case, and there are numerous reports of significant adverse psychological effects in individuals without obvious previous pathology.[68, 69, 104, 120, 220, 259, 272, 307]

A number of clinicians have described an "amotivational syndrome" in some chronic users of cannabis, LSD and other hallucinogens. McGlothlin and West report that clinical impressions suggest that heavy use of these drugs may contribute to some characteristic personality changes, including apathy, loss of effectiveness, reduced drive and ambition, diminished capacity or willingness to carry out complex long-term plans, to endure frustration, to follow routines or to successfully master new material.[209] David Smith

has described a similar condition in a small proportion of chronic users, "The picture in terms of social consequences is then similar to that of a chronic alcoholic, but without the physical deterioration."[278]

While an association between heavy hallucinogen use and an "amotivational" behaviour pattern in some persons is generally acknowledged, the complexity of untangling any causal relationship between the use of drugs and the general life style has resulted in considerable controversy regarding the essential etiology of the syndrome. The role of drugs in such cases may often be more symbolic than pharmacological. Some investigators have suggested a definite organic basis. Unwin contends that "the so-called amotivational syndrome" may in most cases be a "masked depression".[309] Lecker felt that such a syndrome might represent an "operant conditioning state" during which the chronic user aims at the quickest way to get pleasure, and may revert more and more to the drug for instant gratification.[182] McGlothlin has suggested that drug use by persons appearing "amotivational" was perhaps continued and intensified when the drug effects were compatible with the users' natural personality characteristics and preferred life style. He indicated that separating the various social, psychological and pharmacological components would be an arduous task.

In contrast to reports of adverse personality change with hallucinogenic drugs, numerous claims have been made by various LSD users, psychotherapists and scientists that LSD can produce long-lasting beneficial effects on personality and behaviour. Both types of allegation are difficult to evaluate, since few adequately controlled investigations have been done on the long-term effects of either medically supervised or non-medical LSD use. Experimental data suggests that in most subjects, long-lasting effects (beneficial or harmful) of LSD administered under controlled conditions are minimal.[204, 206] Less information is available on non-medical use. It would appear, however, that under some circumstances LSD can potentiate or facilitate attitude and behaviour change, the nature of which is strongly influenced by suggestion, expectation and other aspects of the set and setting, as well as the personality of the individual involved. The degree to which any personality or behaviour change is viewed as beneficial or adverse depends on personal and social attitudes and norms. What is considered positive by some individuals or groups may be viewed negatively by others. Additional research is needed regarding the psychological effects of chronic hallucinogen use—especially in adolescents. Concern has frequently been expressed regarding the effects of regular hallucinogenic drug use on the maturation process in young people, but little systematic data are available.

Some observers warn that chronic hallucinogen use may cause prolonged disruption of cognitive functioning and school performance. While users of LSD and related drugs have been shown in several studies to have poorer academic records than non-users, this general pattern typically holds for all drugs including alcohol and tobacco, and is likely not a pharmacological effect.[15, 88, 107, 273, 274, 275, 316, 321]

Prolonged psychoses are quite rare in clinical or experimental settings, even when psychiatric patients are used as subjects. In 1959 Cohen surveyed 44 investigators who had given LSD or mescaline to approximately 5,000 persons a total of about 25,000 times.[65] He found that psychotic reactions lasting over 48 hours occurred in 0.18% of the psychiatric patients studied and 0.08% of the experimental subjects. Only a few "flashbacks" were noted. There were four suicides among the patients, all occurring months after the LSD experience, and none among the experimental subjects. Whether these deaths can be attributed to LSD use is not certain.

In 1970 Malleson surveyed 73 doctors known to have used LSD on human subjects in the United Kingdom.[200] The data covered some 4,300 patients given a total of 49,000 LSD sessions, and 170 non-patient experimental subjects administered LSD on 450 occasions. There was a reported suicide rate of 0.07%, and a rate of 0.9% for psychoses lasting for more than 48 hours. The investigator concluded that:

> . . . treatment with LSD does give rise to acute adverse reactions, but if there is adequate psychiatric supervision and proper conditions for its administration the incidence of such reactions is not great.[200]

In 1971 the Commission conducted a survey of researchers who had administered LSD (or mescaline or psilocybin) in clinical or experimental settings in Canada over the preceding 20 years.[122] Twenty-four of the 29 investigators surveyed responded and of these, data from 18 research teams were adequate for the following analysis. A total of 3,515 individuals had been administered LSD alone or in combination with other drugs on 5,398 occasions. The vast majority of these subjects were psychiatric patients and were receiving the drug as part of a program of psychotherapy. Sixteen severe psychotic reactions were reported to have occurred in conjunction with LSD treatment (0.3% of drug sessions). The majority of the psychotic reactions lasted for several hours or less, but a few were more prolonged. Three occurred during the year following LSD treatment, and in one case a psychotic reaction lasting almost a year was precipitated three weeks after LSD was administered. Only a few "flashbacks" were noted. Six possible suicides (three confirmed) were reported in patients within a period of two years after LSD sessions. The role of the drug treatment in these deaths was not certain. As with the Cohen and Malleson studies, it is not clear whether the suicide rates found in these patients after LSD treatment were lower or higher than in comparable patients not given such treatment.

McGlothlin and Arnold conducted a ten-year follow-up study of persons who had been given LSD in a controlled medical setting.[204] Some of these individuals also had some non-medical hallucinogen experience. Twenty-five per cent of 247 respondents had experienced a 'bad trip' at one time or another. Almost half of those reporting having had at least one unpleasant experience, viewed them as beneficial in retrospect. Few serious problems were associated with LSD experience.

It would appear, on the basis of these studies, that adverse reaction to LSD is not a prohibitive danger when the drug is administered in a controlled clinical setting. Many other investigators have also indicated that the experimental use of LSD in a medical setting is comparatively safe from a psychiatric point of view.[74, 127, 185] There is no evidence that clinical research with LSD or pharmacologically similar compounds should be restricted for reasons of subject safety. These findings do not provide a satisfactory basis for estimating the effects of illicit use, however, since set, setting, purity and quantity of drug, and consequently, the quality of the experience are all apt to be quite different in these situations.

There are no adequate data regarding the frequency with which various unpleasant or adverse effects occur in the illicit hallucinogen-using population as a whole. These various possible negative effects are rarely clearly defined in studies, but it would appear that a large proportion of regular hallucinogen users have experienced unpleasant effects of some kind. Very little is known regarding the incidence of the more severe reactions or 'freak-outs'.

In a recent survey of Toronto high school students, 53% of LSD users reported that they had experienced unpleasant effects or a 'bad trip' of some kind. Few reported more than one or two such experiences. As would be expected heavy users reported having had a greater number of unpleasant experiences.[274] Solursh reported that 24 'freak-outs' occurred out of 601 'acid trips' in a series of illicit users studied retrospectively.[285] In the Commission's national surveys, approximately one-fifth of the respondents who reported that they had quit or decreased LSD use indicated having had a bad experience as a reason for this change in drug use.[174, 175, 176]

Smart and Fejer of the Addiction Research Foundation have examined the relationship between non-medical drug use and experience in psychotherapy among high school students in a semi-rural area of Ontario.[87] For all drugs (including alcohol and tobacco) significantly more users than non-users had received treatment for psychological problems. Non-users who had received treatment noted family or school problems most frequently as the reason for treatment. Users of illicit drugs most often gave depression as the reason for therapy. It is difficult to ascertain the role of hallucinogen use in these data since the incidence of psychotherapy generally increases with age, as does drug use. The investigators point out that age differences may be a confounding factor in the correlation between drug use and treatment. As well, we do not know whether the treatment preceded or followed hallucinogen use.

In a study of Harvard seniors, Walters and associates found more visits to a psychiatrist among those students who were users of hallucinogenic drugs. However, in half of these cases, the individuals were not users at the time they saw the psychotherapist. Few felt that drug use was related to their seeking psychiatric help.[316] Similarly, a study of adults in the San Francisco area found that hallucinogen use was more common among those who had seen a professional psychotherapist.[154]

A number of surveys of clinicians and treatment services have been reported. As noted in A.1 *Introduction* the interpretation of such studies is generally quite difficult.

In spite of various methodological problems, it is apparent from these surveys that a significant number of adverse reactions to hallucinogens come to the attention of medical authorities.[115, 215, 223, 226, 307] Since most cases of adverse reaction are probably not brought to medical attention, accurate diagnostic and treatment statistics must be considered underestimates of the overall incidence of the less severe conditions. In any event, drug-related cases must ultimately be interpreted in terms of the overall patient population, and more importantly, in terms of the extent and patterns of drug use in the general population from which the patients were drawn.

The statistics collected by the Federal Poison Control Program provide some general information regarding adverse reactions and poisonings attributed to LSD and related drugs.[48, 169,[f]] However, it is generally not possible to distinguish between psychological adverse reactions and physical toxicity from these reports. Since physical reactions to LSD requiring medical treatment are rarely noted in the scientific literature, it is likely that the LSD cases reported are almost entirely psychological 'bad trips' of one sort or another. This may not be the case with MDA or PCP, since these drugs are more likely to produce signs of physical toxicity, which may account for some proportion of any adverse reactions associated with these drugs. For sake of convenience, all of the adverse reaction and poisoning reports are discussed here; physical toxicity and fatalities are dealt with later in the section on physiological effects.

The general increase in the number of hospitals participating in the Poison Control Program from year to year precludes accurate comparisons among the various years, but some interesting relative reporting trends are apparent. (See Table A.3.) The overall number of adverse reaction reports involving hallucinogens is levelling off. The proportion of these cases ascribed to LSD has markedly declined from 1969–1971, as the proportion of cases attributed to MDA, mescaline, and unspecified hallucinogens increased. The specific sub-categories must be interpreted with caution, however. Drug identification in hospital reports involving hallucinogenic drugs is nearly always based on the verbal report of the user, rather than on chemical analysis of the drugs involved, and erroneous classification of such cases frequently occurs. Samples of the drugs taken are not usually available for chemical analysis, and accurate screening for these drugs in body fluids is beyond the capacity of most hospital laboratories.

There has been no mention of adverse reaction to PCP in the Poison Control Program reports. As discussed earlier, PCP is almost invariably represented as some other drug on the illicit market and is rarely acknowledged as PCP. If PCP adverse reactions occur, they would likely be mistakenly attributed to other drugs, or left unspecified. Although alleged 'mescaline'

TABLE A.3

LSD AND OTHER PSYCHEDELIC-HALLUCINOGENS NOTED IN THE POISON CONTROL PROGRAM STATISTICS

	1969*	1970*	1971†
LSD	390 (93.5%)	885 (77.2%)	799 (62.2%)
MDA	7 (1.6%)	53 (4.6%)	151 (11.7%)
Mescaline	15 (3.5%)	57 (4.9%)	105 (8.1%)
STP	3 (0.7%)	15 (1.3%)	3 (0.2%)
PCP	0 (0.0%)	0 (0.0%)	0 (0.0%)
Psilocybin	1 (0.2%)	0 (0.0%)	0 (0.0%)
Unspecified	1 (0.2%)	135 (11.7%)	225 (17.5%)
TOTAL:	417	1,145	1,283

* *Poison Control Program Statistics*. 1969, 1970. (Table G-II)

† Unpublished information provided to the Commission by E. Napke (Head, Drug Adverse Reaction and Poison Control Section, Department of National Health and Welfare, Ottawa.)

is not uncommon in Canada, as indicated earlier, samples of such materials have almost invariably been found upon chemical analysis to be some other drug—primarily LSD, PCP or both. Consequently, it is likely that most of the 177 'mescaline' cases reported actually represent adverse reactions to LSD and/or PCP. Many of the unspecified cases are probably attributable to these drugs as well.

Overall, males outnumbered females by almost three to one in these data, and the vast majority of the individuals involved were in their teens or early twenties. Of the 1,653 reports where the disposition of the case was specified, 15.6% were hospitalized for treatment and these patients received a median of 1 to 2 days institutional care[169] Less than one-tenth of the hospitalized individuals (1.4% overall) were given more than two weeks of in-patient care. It would appear from these data most adverse reactions to LSD and related drugs are of short duration, not requiring hospital care; long-term hospitalization is uncommon.

In the Commission's national survey of psychiatric hospital diagnostic records, taken in the spring of 1971, LSD and related drugs were mentioned as factors in the primary and secondary diagnoses of 67 (0.3%) and 14 (0.06%) respectively of the 22,885 patients in the hospitals surveyed.[121, [d]] In British Columbia, psychiatric wards in general hospitals were surveyed as well, and in this population, LSD-like drugs were mentioned in the diagnostic records of 10 (3.3%) of 293 resident psychiatric patients. A follow-up examination of certain specific case histories was done, focussing primarily on cannabis, although other more general information was obtained as well. These case histories revealed that most of the hallucinogen cases had intense involvement with a variety of drugs, the most common being cannabis, alcohol, 'speed' and LSD. In many instances drugs were apparently considered causal factors primarily because of general information that the

patient had been a user, either in the past or at the time of hospital admission. The inclusion of such cases would likely give an inflated estimate of the role of the drugs in psychiatric disorder. On the other hand, many patients have drug-related problems which are not detected in the admitting diagnoses, and can only be identified by intensive subsequent exploration.[162] Consequently, diagnostic record sampling is bound to miss certain valid drug-related cases. Almost half of the patients in the follow-up study had been diagnosed schizophrenic at some time, and a high proportion of personality problems and adolescent adjustment difficulties were also noted. In many cases, these problems preceded hallucinogenic drug use. (See also Table A.7 in the Annex to this appendix.)

In the 1970 national mental health data provided to the Commission by Statistics Canada, 226 (0.44%) of the first admissions and 71 (0.14%) of the readmissions to psychiatric wards and institutions were attributed to drug dependence involving LSD and related hallucinogens (ICD-304.7).[51, 243, e] For 1971 the corresponding figures were 142 (0.26%) and 62 (0.12%) for first admissions and readmissions respectively. The apparent reduction in hallucinogen cases is striking; however, only limited between-year comparisons can be made with the available data. Some additional toxic reactions to these drugs are undoubtedly included in other undifferentiated general diagnostic categories (e.g., ICD-294.3, 309.1[49]). In the available data, males outnumbered females by approximately three to one. (See also Tables A.5 and A.6 in the Annex to this appendix.)

The Commission psychiatric hospital survey and the national mental health statistics can only provide a general picture regarding the extent to which these drugs are involved in hospital admissions. Detailed follow-up of individual cases would be necessary to ascertain the nature of the role of the drugs in these patients.

While the psychiatric hospital statistics do not allow firm conclusions regarding the causal role of the drugs in the cases described, the data indicate, however, that hallucinogens do appear as a complicating factor in a significant number of psychiatric admissions in Canada. However, such cases apparently represent a very small proportion of hallucinogen users in general, and of the psychiatric hospital patient population in particular.

In studying psychiatric patient populations we have *a priori* defined the group under study as pathological. Consequently, only limited information can be gained from tabulating the pathology within such groups. Such studies provide little information regarding the frequency of adverse reactions in the general population of hallucinogen users. Few controlled studies exist of hallucinogen users who were selected on some non-pathological or non-deviant basis. It would be preferable to compare a cross-sectional sample of hallucinogen users with a control group of non-users with similar social, economic, and educational backgrounds. Even this type of investigation can only demonstrate factors which are associated with drug use and cannot indicate causality.

Although good epidemiological data are lacking, many observers feel that the frequency of psychopathology in the chronic hallucinogen-using population is higher than would be expected by chance. If this were true, at least three reasonable explanatory hypotheses might be adequate, each with some supporting evidence:

(1) Pathological persons may be more likely to use hallucinogens (or to use them heavily). This might, for example, represent acting-out or rebellious behaviour, attempted self-treatment, poor judgment, or an inability to find pleasure by other means.

(2) Hallucinogen use may lead to an increased incidence of psychopathology. This could be a direct neurological effect, or, for example, the drug might conceivably precipitate or complicate a schizophrenic reaction in a predisposed person.

(3) Other factors may influence both psychopathology and drug use. Social alienation, adverse socio-economic conditions, or poor family environment might play such a role.

In summary, mild transient phases of anxiety and paranoia occur in some inexperienced and regular users of hallucinogens in North America. More severe panic reactions, especially among inexperienced users have been reliably reported. The notion that LSD and related drugs may, under certain circumstances, precipitate a more prolonged psychotic reaction in predisposed individuals is gaining some support in the clinical literature, although there is no consensus as to the exact nature of the predisposition or its prevalence in the general population. Other more prolonged adverse psychological reactions to chronic use (including personality changes and an "amotivational syndrome"), in some instances in apparently previously normal individuals, have been cited, but there is considerable controversy as to the validity and general applicability of many of the clinical reports presented. It is not yet certain what role the drugs play in such chronic syndromes or the frequency with which they occur in the hallucinogen-using population. Additional epidemiological research will be necessary to clarify these issues. (Further discussion of theoretical and methodological issues relevant to hallucinogen adverse reactions appears in Chapter Two of the *Cannabis Report*.[48])

Physiological Effects

LSD exerts its most significant physiological effects on and through the central nervous system, although the exact mechanisms by which this occurs are not yet known. As a result of its potent general arousal or activation capacity, LSD may produce a variety of autonomic nervous system (sympathomimetic) actions, generally considered to be of little clinical significance at normal doses. Commonly noted are minor increases in heart rate, blood pressure, blood sugar level, body temperature and perspiration. Chills, 'goose pimples', flushing of the facial skin, decreased or increased urination,

headache, nausea and, more rarely, vomiting are reported. Nausea is more common with peyote than with LSD. LSD may produce a variety of changes in the visual system, including widening of the pupils, some disturbance of focussing and accommodation, an increase in intra-ocular pressure, and certain direct effects on the retina. It would appear that the profound changes in visual perception which typically occur reflect a combination of peripheral (perhaps retinal) and central neural mechanisms. LSD and most of the related drugs generally increase the activation of the brain (as indicated by the EEG), produce alertness, block sleep, decrease appetite, change respiratory patterns, facilitate certain simple reflexes, and may induce tremors and reduce coordination. A few rare cases of convulsions have been reported.[21, 25, 27, 67, 131, 141, 142, 195, 255] Cold extremities are sometimes reported with LSD and are likely due in part to constriction of the blood vessels in the skin. There have been occasional rumours of gangrene in the extremities allegedly caused by the use of poorly synthesized illicit LSD (thought to contain other physiologically active ergot alkaloids). We have been unable to substantiate these rumours, but one case of gangrene was recently reported in which LSD and large doses of nicotine (a potent vasoconstrictor) were implicated.[139]

Considering their close structural similarity with amphetamine, it is surprising that MDA and STP produce little amphetamine-like peripheral physiological change. Pupilary dilation is the only conspicuous effect of MDA at low doses. Larger doses may produce increased perspiration, dry mouth, tension, tremors, dizziness, indigestion and occasionally nausea. Appetite is usually suppressed. Amphetamine-like central stimulation and EEG changes occur. [12, 100, 134] Although the literature is inconsistent regarding the physiological effects of STP, it would appear to be similar to, but more potent than MDA in most respects.[85, 96, 281]

At moderate doses, PCP produces physiological effects similar to alcohol or barbiturate intoxication. Larger doses are increasingly anesthetic, but very high doses produce convulsions. Moderate doses typically result in numbness in the extremities, an increase in blood pressure, heart rate, perspiration and salivation, and dilation of the peripheral blood vessels in the skin. Unlike most LSD-like drugs, PCP produces a slowing of the EEG, generally decreases arousal, and does not affect pupil size. Muscular incoordination, ataxia, blurred vision, minor changes in involuntary eye movement, and dizziness are often reported. Nausea and vomiting may occur.[24, 78, 79, 127, 234]

There is no direct evidence of generalized brain damage due to the chronic use of LSD and related drugs, but indications of impairment on some behavioural tests have been reported which are suggestive of slight neurological dysfunction in certain LSD users.[28, 39, 70, 205, 326] The evidence is not consistent in this regard, and further research is needed. There are no data available on the neurological consequences of long-term use of MDA or PCP in humans, but existing animal studies do not indicate cause for concern at moderate doses.[78, 134, 234]

Chromosome and Birth Effects

A few years ago, considerable controversy and sensational publicity arose around the possibility that LSD might affect hereditary transmission through chromosomal alterations, produce changes in white blood cells resembling leukemia, or adversely affect the developing human fetus.[60, 147, 155] Related studies, involving test-tube preparations of human cells, live animal and insect experiments, and examinations of illicit drug users, are contradictory and provide no final answers to these important questions.[25, 81, 101, 136] The relationship between *in vitro* (test-tube) and *in vivo* (living organism) effects is rarely straightforward, and generalizations from one animal species to another are difficult. Furthermore, studying the users of 'street' drugs gives little information regarding specific compounds, since such individuals typically use a variety of drugs, and neither the investigator nor the subject can be sure of the purity, quantity or identity of substances obtained from the illicit market. In controlled human studies, in which chromosomes were examined before and after clinically supervised administration of known doses of pure LSD, little evidence of significant change was noted.[8, 72, 137, 300] The effects of prolonged frequent use of LSD have not been directly investigated in the laboratory, however, and the presence or absence of chromosomal alterations with heavy use of illicit materials can not be predicted on the basis of present information.

Research on chromosome changes is complicated by the fact that temporary or permanent chromosome breakage is not an uncommon response to a variety of non-drug experiences, and can be produced by nuclear radioactivity, x-rays, many pollutants, fever and a number of virus infections. Furthermore, there is evidence that a number of commonly used drugs, including caffeine and aspirin, may cause chromosome breaks in certain cells.[158, 262, 292, 323] It should be noted that chromosome damage *per se* does not necessarily affect either the individual or his offspring, although the possibility must be considered. There is considerable controversy regarding the frequency of occurrence of various chromosomal abnormalities in the general population.[271]

High doses of LSD administered at certain times early in pregnancy have been shown to produce deformities in the offspring of some animal species but not others.[10, 17, 84, 102, 250, 311, 317] No unequivocal evidence of such teratogenic LSD effects in humans has been reported, although there have been a number of widely publicized instances of early abortion or abnormalities in babies born of mothers who had used LSD.[40, 43, 52, 82, 147, 148, 300] Whether such anomalies occur more frequently in LSD users than in similar or matched non-users is uncertain.[2, 208, 291]

Recent reviews of the literature suggest that LSD does not cause lasting chromosome breaks *in vivo* and that it does not produce cancer or birth deformities in humans.[17, 76, 99, 192] However, many investigators still feel that the possibility of chromosome or fetal damage in humans forbids the use

of LSD and related drugs, for either medical or non-medical purposes, by women who are either pregnant or expect to become so in the near future.

Physical Toxicity and Death

Human fatalities due directly to LSD overdose are unknown in the scientific literature. In terms of lethal physical toxicity LSD must be considered one of the safest drugs known. Mention of psilocybin or mescaline deaths in the literature is rare, as well. We have found no evidence of overdose deaths involving these drugs in Canada.[123, 271, [s]]

Little data is available on the lethal toxicity of PCP in humans. There is no evidence in the scientific literature or from the Commission's studies of drug-related deaths that severe PCP overdose is a likely occurrence. We have not been able to document any such fatalities in Canada.[217] No PCP poisonings have been recorded as such in the Federal Poison Control Program statistics.[48] However, as noted earlier this may represent drug identification and classification errors rather than a lack of toxicity, since, in Canada, PCP is almost invariably sold as some other drug on the illicit market. While similar misidentification of drugs may exist in death records, such an error is less likely to occur since greater care is normally taken to chemically identify drugs in fatal cases. However, even in these latter instances, screening for drugs is usually not extensive or complete.[217]

The toxicity of MDA has been studied in animals, but little information is available regarding lethal levels in humans.[57, 134, 240] Because of the close chemical and pharmacological similarities between MDA, mescaline and the amphetamines, and the rarity of overdose deaths with these latter compounds, it would seem reasonable to expect a similar lack of fatalities associated with MDA. Animal studies suggest that MDA and amphetamine have comparable lethal toxicity.[12] Correspondingly, until recently, MDA overdose deaths were not mentioned in the literature. The Commission's survey of provincial coroners has provided information on 18 MDA-related deaths in Canada during the years 1969–1972.[123] (Five of these cases have been described by Cimbura.[57]) Eight of the 18 cases involved other drugs as well, but in the remainder, MDA was the only drug found in the body. In several cases samples of the drug taken were available for analysis and were found to be relatively pure MDA, without significant adulteration or contamination. The majority of the fatalities involved oral use, although evidence of intravenous administration was noted in some instances. The actual mechanism of death was generally uncertain. Although the actual doses involved cannot be accurately determined, the coroners' reports noted a range from "one capsule" as a minimum, up to 60 capsules in one instance, and one-quarter ounce in another. It would appear that in most cases massive doses were involved. Sixteen of the individuals were males, and all were between 15 and 34 years of age.

Because of classification ambiguities, it is not possible to obtain information on MDA-specific fatalities from the death statistics published by Statistics Canada.[50] As noted earlier, the Federal Poison Control Program has reported 151 cases of MDA toxic reaction poisonings in 1971, but in most instances it is not possible to determine to what extent these cases represent psychological adverse reactions or physical toxicity.[221] However, five of the MDA-related poisonings were fatal; three of these cases involved opiate narcotics as well. Very recently there have been several reports of deaths attributed at least in part to PMA (paramethoxyamphetamine) in Canada and the United States.

MDA is unique in that it appears to be the only one of the common psychedelic-hallucinogen or stimulant drugs which seems to involve a significant risk of fatal overdose as these drugs are presently used in Canada. Further research is needed to determine what combination of behavioural and pharmacological factors are involved in this unexpected phenomenon.

Tolerance and Dependence

Tolerance to the psychological and physiological effects of LSD develops rapidly on repeated use, although the form of psychological tolerance is unusual in several respects. Tolerance to most drugs can be overcome to a certain extent by simply increasing dosage. With LSD, often a period of several days must separate 'trips' if the full effects are to be obtained, regardless of dose.[141, 143] A second unusual quality of LSD tolerance is the rapidity with which it develops and dissipates. A reduction in intensity of the effects occurs after only a few consecutive administrations[5] and tolerance is lost within a few days of last use. Furthermore, when LSD is used intermittently many users report a 'reverse tolerance', or increased sensitivity to the drug and may, after experience, require less of it to achieve the desired effects. These factors suggest that the pharmacological mechanisms underlying LSD tolerance are quite different from those seen with most other psychoactive drugs. Cross-tolerance exists between LSD and some related drugs, and an individual who has recently taken LSD will generally show a reduced response to mescaline and psilocybin, but not to PCP or cannabis.[23, 144, 324]

Physical dependence does not develop to LSD, even in cases in which the drug has been used more than two hundred times in a single year.[69] Psychological dependence has been reported to occur in certain individuals who become preoccupied with the drug experience and feel emotionally depressed and unsatisfied without it. Normally, however, LSD use is intermittent and periods of weeks or months may separate 'trips' in even confirmed users. Chronic frequent use is very rare.

Because of the general sedative properties of PCP, some degree of tolerance and physical dependence might be expected with daily use, but little human data is available. There is evidence that tolerance develops to

some of the effects of STP.[133] Similar effects apparently occur with MDA. There is no data available regarding physical dependence on MDA or STP, but an amphetamine-like rebound response might be expected with these drugs after repeated use. The typical patterns of occasional or intermittent use of LSD-like drugs makes the development of physical dependence highly unlikely under most conditions.

Hallucinogens and Other Drugs

Amphetamine is reported to intensify, prolong or otherwise alter the experience produced by LSD and related drugs. Chemical analysis of illicit drug samples suggests that such mixtures are not often used, however. LSD and PCP often appear in combination in illicit samples, yet little is known as to how these drugs interact in humans. They produce opposite effects on many physiological functions, and animal studies indicate that LSD and PCP are antagonistic in some respects.[78] Further research into LSD-PCP interaction is needed.

The psychological effects of LSD, MDA and most related drugs are reduced significantly by chlorpromazine (Largactil®), a phenothiazine major tranquilizer, and to lesser degrees by barbiturates, minor tranquilizers and other sedatives. In rare instances phenothiazines may potentiate the LSD response. Niacin, niacinamide, succinate and glucose have also been reported to reduce some of the effects of LSD.[64, 127, 153, 260] There are no confirmed antagonists of PCP, but there is some suggestion in the literature that certain psychological effects may be reduced by succinate, and that PCP sedation may be blocked by amphetamine.[79, 237]

When STP first appeared on the illicit market in California, toxic effects were reportedly potentiated by chlorpromazine given in treatment of adverse reactions. This gave rise to widespread warnings against the use of chlorpromazine in treating 'bad trips'.[277] However, in subsequent laboratory studies involving chemically pure DOM, chlorpromazine clearly did not accentuate the effects of DOM, but lessened them to some degree.[133, 281] However, the interaction of chlorpromazine and DOM over a wide dosage range has not been explored. It has been suggested that the unidentified drugs originally responsible for the alleged STP-chlorpromazine potentiation were actually atropine-like compounds rather than, or in addition to, DOM.

Antibodies to LSD and certain related drugs have been developed, in part for use in immunoassay techniques for the detection of drugs in body fluid and tissue.[72, 312] Recently, such antibodies were shown to reduce the response to LSD in an animal study—thus demonstrating the possibility of immunization against hallucinogenic drug effects.[313]

Users of LSD typically also use a variety of other psychotropic drugs. Almost all LSD users have smoked cannabis, but only a minority of persons who have tried cannabis have also taken LSD. Heavy cannabis users are more likely to have tried LSD than are occasional users. A significant pro-

portion of young users of speed or opiate narcotics also report previous use of LSD and related drugs. LSD is apparently not very popular among regular heroin or speed users, however.[56, 108, 174, 175, 176, 207, 253, 274] (See also Appendix C *Extent and Patterns of Drug Use.*)

A.6 ALCOHOL

INTRODUCTION

Alcohol is one of the most widely used psychoactive drugs known to man; it has apparently been with us since the dawn of civilization. Breweries flourished in Egypt almost six thousand years ago, and there is evidence that Stone Age prehistoric man made alcoholic beverages long before that.[14, 283] The Roman philosopher Seneca, in an essay on alcohol, observed almost 2,000 years ago that "Drunkenness is nothing but a condition of insanity purposely assumed."[264] Varying degrees of alcohol use have appeared in most societies throughout recorded history and have traditionally played an important symbolic as well as pharmacological role in many social, religious and medical practices. Just as the use of alcohol has been almost universal, so, apparently, has its misuse. Consequently some degree of opposition to 'drink' appears to have arisen in all indulging cultures, although attempts to eradicate its use have met with almost uniform lack of success.

What is this drug which has been hailed as the "water of life" and "nectar of the gods" by some, and damned by others as "second only to war" as a source of human problems? Ethyl alcohol (C_2H_5OH) is a colourless, flammable and volatile liquid made up of three common elements, carbon, hydrogen and oxygen. The word "alcohol" is commonly taken to mean *ethyl alcohol* or *ethanol* (common beverage alcohol), even though there are a vast number of other substances in the aliphatic alcohol family, many of which are highly toxic in even low doses. Methyl alcohol (wood alcohol) and isopropyl alcohol (rubbing alcohol) are common examples of such toxic substances. Unless otherwise specified, in this report the word "alcohol" is taken to mean ethyl alcohol or ethanol.

Although the technique of producing alcoholic beverages by fermenting fruit, grain, vegetables, and other food-stuffs has been known for the past few thousand years, the biologic process by which the drug is generated was first illuminated by Louis Pasteur in the middle of the 19th century. His investigations revealed that alcohol is produced by single-celled microscopic plants (yeast fungi), which break down certain sugars by metabolic combustion, releasing carbon dioxide (CO_2) and ethyl alcohol as by-products. The production of CO_2 is responsible for the head on a glass of beer, the popping of champagne corks, and the leavening effect of yeast in the rising of bread. Since yeast cannot digest starch, mash from cereal grains such as barley, rye, corn and rice must be malted (i.e., converted to maltose

sugar) prior to fermentation in the production of beer, gin, whisky and other alcoholic beverages.

Under optimal conditions fermentation continues until the sugar supply is exhausted. However, as the amount of alcohol in the fermenting solution increases, the metabolic activity of the yeast is slowed and arrested, and the fungi are killed when the alcohol they produce reaches a level of about 14%. Thus a limit is set on the maximum strength of natural (undistilled) beverages such as beer, wine and cider. The distillation process of boiling off and isolating the more volatile alcohol from the other fluids (mostly water) allows a further increase in ethanol concentration. Although this technique was used in Middle Eastern cultures centuries earlier, the production of 'spirits' by distillation has been known in Europe for less than seven hundred years. Today, alcohol can be produced synthetically.

The pharmacological effects of alcoholic beverages are attributable primarily to the quantity of alcohol they contain. In Canada, beer usually contains about 5% alcohol by volume, natural wine 7% to 14%, fortified wine up to 20%, and distilled spirits or liquor approximately 40% alcohol. In other words, a 12-ounce bottle of beer or 3 to 4 ounces of wine contain about as much alcohol as 1¼ ounces of whisky. In the alcohol literature a distinction has frequently been made among beverages on the basis of potency, with more serious consequences often attributed to the use of distilled liquor than to the consumption of weaker drinks such as beer or wine. However, certain studies, including some Commission research, suggest that even though acute toxic reactions may occur more frequently with distilled spirits, the long-term effects of chronic alcohol use are primarily related to the total alcohol consumed, rather than to the form or potency of the individual drinks.[89, 151, 222, 279] Further research in this area is clearly needed.

In addition to ethanol and water, alcoholic beverages frequently contain small quantities of substances collectively referred to as *congeners*. Typical congeners include methanol, higher alcohols (fusel oil), acids, esters, aldehydes and other organic and inorganic compounds. Some of the congeners are important to the flavour and aroma of alcoholic beverages. There is evidence that they also can contribute to certain effects including post-intoxication 'hangover'. After pure ethyl alcohol and water (e.g., *Alcool*) which has essentially no congeners, vodka has the second lowest congener content of all alcoholic beverages. At equivalent doses of alcohol, after-effects with these beverages are less severe than those produced by drinks with more congeners, such as brandy.[43, 64, 202, 215]

The notion of alcohol 'proof' originated centuries ago from a crude but effective analytic technique designed to assess the strength of spirits. If gun powder soaked with the beverage exploded on ignition, this was taken as 'proof' that the liquor was more than half alcohol. 'Proof spirit' in the United Kingdom and Canada contains about 57% alcohol, while in the United States proof is calculated as twice the percentage of alcohol per unit volume of the beverage (e.g., 80 proof whisky is 40% alcohol).[74]

Canada has experimented with alcohol prohibition in varying ways since 1878. Although there are currently some 'dry' localities, alcohol is generally legally available to adults across the country. Over 300 years ago the prohibition of liquor sales to Indians was Canada's first alcohol regulation.[20] Some residual discriminatory policies have only recently been eliminated.

In the United States there was a 15-year period of alcohol prohibition which ended in 1934. Although alcohol consumption and certain related social problems and physiological disorders (such as cirrhosis of the liver) decreased during "prohibition", the program was repealed, apparently because of the unworkable form of the laws, inadequate enforcement, corruption among public authorities and, perhaps most importantly, a general lack of public support. During that period, the elimination of legitimate alcohol outlets resulted in home breweries and distilleries, the production of 'bootleg' liquor, the use of toxic substitutes, smuggling (frequently from Canada), and an economic vacuum which was rapidly filled by organized crime. Many authorities feel that this multi-million dollar illicit market provided the initial capital for the emergence of a network of syndicated criminal and quasi-legal business empires which have considerable economic and political strength in North America today.

Alcohol is now used by approximately three-quarters of the Canadian population over the age of 18. (See Appendix C *Extent and Patterns of Drug Use.*) Although most alcohol is undoubtedly consumed for its pharmacological properties, there is a significant aspect of alcohol usage which is in some respects independent of direct drug effects. There are many longstanding customs, traditions and superstitions which pervade alcohol use in the Western world. Because it has become an integral part of our culture, the set and setting surrounding alcohol use is substantially different from that associated with the non-medical use of other drugs in Canada.

Drinking alcoholic beverages may have special meanings in various social contexts. Depending on the type and quantity of beverage consumed, alcohol use is often symbolically associated with the acknowledgement of birth, death, marriage and other contracts, adulthood, friendship, and, to some, it may imply virility or masculinity, affluence and cultural refinement (or the opposite). Although it is employed in some religious ceremonies, in other contexts many individuals may approach its use with moral apprehensions and feelings of ambivalence and guilt. Some reject it outright on principle, while others feel that moderate use is morally acceptable. In many social circles abstinence is frowned upon and 'teetotallers' are looked upon with suspicion. But alcohol intoxication is frequently tolerated, condoned, and even expected and encouraged in many situations in North American society. When one considers the fact that these various attitudes interact with the diverse pharmacological potentials of alcohol in determining the overall drug effect, the complexity of the psychopharmacology of alcohol

becomes apparent. Because its use is so ingrained at all levels of society, many Canadians do not consider alcohol a drug.

In a wider context Jaffe observed in *The Pharmacological Basis of Therapeutics:*

> The large role that the production and consumption of alcoholic beverages plays in the economic and social life in Western society should not permit us to minimize the fact that alcoholism is a more significant problem than all other forms of drug abuse combined.[135]

Medical Use

Alcohol is currently recognized as an official drug in the British and U.S. Pharmacopeias, although the various alcoholic beverages, as such, are no longer listed for medical use. Alcohol has been cited over the past few thousand years as a cure for nearly every ailment or disease. Most of the medical benefits were probably indirect, if not more imagined than real, and although it still plays a useful role in medicine, many of alcohol's legitimate therapeutic functions have now been filled by more effective drugs.

Alcohol is often used as a preservative, solvent, and vehicle for other drugs, and is contained in tinctures, elixirs, spirits and many medicinal syrups. External applications are used to cleanse, disinfect and harden the skin, to reduce bed sores, to cool fever, and to decrease sweating (alcohol is included in many antiperspirant deodorants). In concentrations around 70%, alcohol is an effective anti-bacterial agent, although it is not satisfactory for disinfecting open wounds since it damages the raw tissue.[74, 237] Alcohol is sometimes injected in the vicinity of nerves to temporarily or permanently block transmission and relieve certain types of pain. Concentrated alcohol may be administered orally in the treatment of fainting, and alcoholic beverages are sometimes used to stimulate appetite and digestion. Alcohol is also sometimes employed as a source of calories and may be administered orally or intravenously in such applications.

Alcohol is still sometimes recommended as a tranquilizer, sedative, or hypnotic and may also serve as a mild mood elevator for some individuals. Used alone it has not been considered a safe surgical anesthetic, since the dose necessary to produce unconsciousness is often dangerously close to the fatal level. However, the use of alcohol, particularly in conjunction with other anesthetic drugs, is being re-evaluated.[59, 60] In addition, alcohol may reduce pain at moderate doses. Alcohol is still used in household medicine to "treat" the common cold, although its benefits, if any, are probably limited to an improvement in mood and increased relaxation and rest.

Chemical Analysis of Illicit Samples in Canada

Most of the alcohol consumed illicitly in Canada comes originally from licensed brewers and distributors. However, thousands of gallons of liquor

are illicitly manufactured and consumed in Canada annually. In some instances considerable effort is made to imitate or counterfeit popular brands, and bottles are often prepared complete with bogus labels and Liquor Board stamps.[30, 85] (See also Appendix B.6 *Sources and Distribution of Alcohol.*)

Among the contaminants which have been identified in illicit alcohol are calcium and copper salts, hydrocarbon oils, vegetable debris, dead insects, animal feces and urine. These materials arise from uncontrolled and usually unsanitary conditions, including easy access for insects and rodents, the use of dirty vessels, hard or unclean water, and abnormally high acid content in the brewing mash. Lead from old radiators used as condensors in stills is occasionally found in illicit alcohol. Deliberate additives include sugar, soft drinks, various flavouring and colouring matter, and glycerol. Toxic quantities of methyl alcohol are sometimes added inadvertently (blindness and death may result from such adulteration). Illicit alcohol is typically diluted with water and the strength of such spirits is highly variable, with approximate limits of 30–160 proof.[87, 111, 115, 243]

Administration, Absorption, Distribution and Physiological Fate

Alcohol is usually taken orally and is rapidly and completely absorbed in the gastrointestinal tract. Some absorption takes place in the stomach, although diffusion into the blood stream is typically most rapid from the upper intestine; consequently, the quicker the alcohol passes through the stomach, the shorter its latency of action and the higher the peak blood alcohol level achieved.[74, 237] Alcohol in beer or sweet wine is absorbed more slowly than that in equivalent quantities of dry wine or diluted or full strength distilled spirit. Therefore, they result in a lower peak effect than the latter beverages.[112, 292] Food eaten before or with alcohol tends to decrease the drug effect by slowing stomach emptying, and a meal before drinking alcohol may reduce the peak alcohol level in the blood by almost one-half compared to that attained by drinking with the stomach empty. Once absorbed, alcohol is distributed quite uniformly in all body fluids; it easily enters the brain, and in pregnant women, crosses the placental barrier into the fetus.[303]

Approximately 95% of the alcohol entering the body is broken down by oxidation and the rest is excreted unchanged, primarily in the urine and breath. Much smaller quantities of alcohol can be detected in sweat, saliva, tears, milk and other body secretions.[237] Unlike many drugs, alcohol is metabolized at a relatively constant rate on a given drinking occasion. The rate of alcohol elimination is roughly proportional to body weight, with the average 150-pound man metabolizing about 9 ml (0.3 oz.) of pure alcohol per hour.[74, 303] On various occasions there can be significant differences in the rate at which an individual metabolizes alcohol. Substantial differences in metabolism rates between individuals are frequently observed. Genetic factors are often significant. Differences in response to alcohol among various ethnic

and racial groups have been linked to differences in rates of metabolism at various stages in the biotransformation of alcohol.[66, 231, 313]

While certain alcoholic beverages, such as beer, contain very small amounts of protein and carbohydrates, alcohol itself provides only calories when metabolized, but no vitamins, minerals, protein or essential fatty acids needed for adequate nutrition. Depending on the form of alcoholic beverage and possible mixers, an ordinary drink may contain 90 to 150 calories or more. Thus, as little as two 12-ounce servings of beer may make up 10% of the daily caloric needs of a 160-pound individual, and a 25-ounce bottle of 40% distilled spirits may supply over 50% of the needed calories.[82, 156, 292]

A convenient index of the quantity of the drug in the body (and the intensity of the short-term effects) is the *blood alcohol level* (b.a.l.), represented in per cent alcohol per unit weight of blood. Since the amount of alcohol excreted in the breath bears a fixed relationship to that in the blood, it is possible to estimate the blood alcohol level from expired air. This principle is utilized in the *Breathalyzer* tests now employed in the enforcement of driving laws.[18, 74, 274, 293] A variety of other related techniques are also available for rapid estimation of blood alcohol level.[165] Standard methods of chemical analysis have been developed for the direct determination of alcohol levels in body fluid and tissue.[46, 126, 127, 278]

Short-Term Effects

Alcohol exerts its primary acute effects through the central nervous system, producing a general sedation or depression of neural activity over a wide dosage range, although in certain circumstances, behavioural and psychological stimulation may result. Little is known as to the specific mechanism by which alcohol produces its psychopharmacological effects. However, in a general sense, alcohol is believed to exert its sedating effects by inhibiting areas of the brain stem reticular formation which control sleep and wakefulness. Behavioural and psychological arousal effects are thought to be related, at least in part, to the release of certain brain areas (including the cortex) from inhibition by the reticular formation. Areas of the brain called the limbic system and the hypothalamus are involved in the neurological basis of mood and emotion; but since the operation of these systems is not at all well understood, it is not possible to speculate how alcohol (or any other drug) might affect them.[136, 139]

As with most drugs, certain effects of alcohol depend to a large extent on the individual and the situation in which the drinking occurs. A drink or two may produce drowsiness and lethargy in some instances while the same quantity might lead to increased activity and psychological arousal in another individual, or in the same person in different circumstances. Furthermore, a dose which is initially subjectively stimulating may later produce sedation.[206, 226, 237].

In many social settings, alcohol seems to result in a lessening of inhibitions, and in feelings of well-being, sociability and camaraderie in most individuals. For many people alcohol relieves tension and anxiety—the common notion that one 'needs a drink' when worried, irritated or upset, reflects a general acknowledgement of this function. Although alcohol usually elevates mood at first, a general lack of emotional control, including anxiety, withdrawal, self-pity and general depression may occur later or with higher doses.

Hostility and aggression are not at all uncommon in some drinkers, and fights and other forms of violent antisocial behaviour are often reported to accompany bouts of heavy drinking. There is evidence that persons with certain pre-existing psychiatric or neurological disturbances are more likely than others to become aggressive or violent when intoxicated.[116, 201, 220, 312] Although delusions, illusions and amnesic 'black-outs' may occur with high doses in some individuals, acute alcohol psychosis (pathological intoxication) in normally moderate drinkers is rare.[98, 130, 247, 280]

Alcohol does not have a specific aphrodisiac (sex-drive stimulating) effect *per se,* although the emotionality and general lessening of inhibitions often induced may lead to an increase in sexual activity and other normally restricted behaviour. An increase in desire or opportunity may be countered by acute sexual impotence or difficulty achieving orgasm.[237, 266, 292]

In moderate amounts, alcohol may increase or decrease heart rate, produce a 'flushing' or dilation of small blood vessels in the skin (giving a sensation of warmth), lower body temperature, stimulate appetite and the secretion of saliva and gastric juices, increase urination, produce a slowing of the electroencephalogram (EEG), increase complex reaction time, and may reduce muscular coordination. The swelling of the minor blood vessels in the eye (conjunctival congestion) may give a 'blood-shot' appearance.[6, 74, 237, 306] Alcohol has been reported to narrow the visual field, reduce sensitivity to brightness contrast, and increase the time required for the eye to adjust to darkness,[158, 197, 248] but other investigators have not found such effects.

Alcohol generally reduces performance on tests of a wide variety of psychological functions. Tasks requiring a high degree of selective or divided attention are particularly sensitive to alcohol effects,[195, 196] and impairment is usually most pronounced on complex and recently learned tasks.[37, 74, 132] However, a small amount of alcohol may actually improve performance in some situations.[293] The frequently observed impairment of psychomotor performance with moderate doses of alcohol (e.g., 0.04% blood alcohol level) was confirmed in Commission experiments.[58, 164, 196, 233, 234, 293]

In high doses, alcohol produces drunkenness with disorientation and confusion, slurred speech, blurred vision, inadequate muscular control and, often, nausea and vomiting. As larger quantities are ingested, depression of respiration, general anesthesia and unconsciousness and, rarely, death due to respiratory and circulatory failure occur.[74, 169, 237]

Heavy alcohol use is often followed by pronounced 'hangover' symptoms characterized by nausea, fatigue and weakness, dizziness, poor coordination, headache, 'heartburn' and a variety of other aches and pains. Anxiety, guilt and depression may also occur. The number and intensity of these symptoms tend to increase in proportion to the quantity of alcohol drunk.[43, 96] Some authorities consider this post-inebriation phase a form of acute withdrawal syndrome.

A number of factors have been shown to influence appetite for alcohol in different species, including age, sex, and various physiological, nutritional and pharmacological variables.[261] Electrical stimulation and specific lesions in certain parts of the brain have been shown to affect alcohol intake and effects in animals.[5, 154, 174] Changes in alcohol self-administration may be mediated by the modification of neurological reactions which reinforce drug use.

Many studies have shown that the use of alcohol is negatively correlated with academic performance in high school and university.[272, 308, 309] Heavy or frequent users of alcohol almost invariably have poorer grades than light users or abstainers. While chronic heavy use might have direct effects contributing to this correlation, non-pharmacological factors are thought to be primarily responsible. Similar findings have been reported for most other drugs, and it would appear that certain attitudes and life styles influence both drug use and academic performance.

Driving

In moderate to large doses alcohol adversely affects many of the functions thought to be important in automobile driving. In addition, to detrimental effects on various perceptual, attentional, cognitive and psychomotor skills, alcohol may increase risk taking and aggression in driving.[47, 162, 284] Commission experimental research has replicated the frequent finding that alcohol in quantities commonly consumed in Canada (0.07% blood alcohol level) reduces driving performance.[13, 48, 105, 189]

In 1904, data linking alcohol consumption to automobile crashes was published in an editorial in the *Quarterly Journal of Inebriety*.[227] Since then, a considerable amount of evidence has been accumulated which continues to point to alcohol as a major contributing factor in such accidents. A 1969 study of alcohol involvement in fatal motor vehicle accidents in three Canadian provinces presented findings similar to those reported regularly across North America: approximately 70% of drivers killed in single vehicle accidents and 50% of drivers killed in multi-vehicle collisions had been drinking. Among all driver fatalities, alcohol was detected in the blood of 60 to 70% of those considered responsible for their own deaths.[26] The majority of such alcohol-related fatalities involve drivers with blood alcohol levels above 0.08%; a much smaller fraction of other drivers on the road at a comparable time show blood alcohol levels of such a magnitude.[17, 166] In other words, many of

the fatal crashes are caused by a small but distinguishable group of drivers, namely those with blood alcohol levels above about 0.08%.

Although more than half of the adult population in North America at some time drive automobiles after drinking, alcoholics, primarily men, account for a disproportionate number of highway fatalities, even when corrections are made for driving exposure.[253, 293, 302] Numerous factors including failure to use seat belts, greater susceptibility to death due to trauma, and possible suicide attempts may contribute to this relationship.[86, 287] Another group which accounts for a disproportionate number of highway deaths, often involving high blood alcohol levels, are young adult males (roughly between the ages of 15 and 24).[26, 216] However, evidence indicates that all age groups contribute to the traffic safety problem, particularly after heavy drinking.[17, 293]

The relationship between blood alcohol level and non-fatal automobile accidents has not been extensively studied, partly because drivers involved in such accidents may not consent to being tested for alcohol. Nevertheless, evidence indicates that blood alcohol levels at or above 0.10% are seen in approximately one-quarter of the serious but non-fatal crashes; for various reasons these figures are considered to be underestimates.[17, 113] Thus, the overall trend is quite consistent—significant quantities of alcohol are frequently found in drivers (and, incidently, in about 50% of their passengers) involved in fatal single-vehicle crashes, fatal multiple-vehicle crashes, and non-fatal serious crashes, compared to drivers not involved in accidents. On the average, the likelihood of such crashes begins to accelerate at blood alcohol levels of about 0.08–0.10%; above that the chance of an accident increases rapidly as a function of the alcohol level in the blood.[17, 119, 166]

Alcohol has also been found to be a contributing factor in pedestrian fatalities;[100] in the Canadian study cited above, more than half the pedestrians killed were shown to have been recently drinking.[26] Alcohol is also a significant correlate of fatal aviation crashes, and it has also been cited as a contributing factor in rail crashes and home and industrial accidents.[22, 54, 100, 107, 159, 293]

Although the intensity of the acute effects of alcohol can, to a certain extent, be estimated from the amount of alcohol in the blood, the relationship between the blood alcohol level and the effects produced may vary considerably from individual to individual. Federal legislation prohibits driving with blood alcohol level greater than 0.08%. This concentration may be produced by three or four ordinary drinks, if consumed in a short time. While certain individuals might be capable of driving satisfactorily with this much of the drug, most persons perform less skillfully at even lower levels.[105, 189] Although the *Breathalyzer* can be used to predict the immediate effects of alcohol, there are no simple methods of detecting a 'hangover', and there are indications that this post-inebriation phase can have adverse effects on psychomotor performance and driving.

Recent reviews of the broad area of drugs and traffic safety have concluded that alcohol is a major factor contributing to highway crashes and fatalities. There is little evidence that other drugs are presently significant factors in comparison.[145, 208, 269, 303] According to Statistics Canada data, almost a half million automobile accidents were reported in this country in 1971; of these, there were 4,670 fatal accidents (resulting in 5,573 deaths), 192,599 traffic injuries and 358,883 property damage accidents.[229] Existing information suggests that alcohol was involved in a large proportion of these occurrences, although Canadian data are not available to allow an accurate estimate of the precise number which could be attributed to alcohol intoxication.[276] It has been estimated that alcohol-related mishaps account for 30% of the severe injuries and at least 50% of the deaths from traffic accidents in the United States.[211, 293, 299] The Canadian situation is probably not drastically different.

Long-Term Effects

Many authorities differentiate between 'low-risk' (moderate) and 'high-risk' (heavy) drinking in discussing the long-term effects of alcohol. For most otherwise normal individuals, moderate drinking over a prolonged period of time may produce little apparent psychological or physiological change. However, high-risk or heavy drinking (e.g., an average of five or more drinks a day) frequently leads to a variety of psychological and physiological difficulties, many of which are subsumed under the general terms *alcoholism* or *alcohol dependence.*

There is considerable disagreement among authorities as to the proper delineation of the concept of alcoholism—definitions may be as general as "a family of disorders accompanying chronic heavy drinking" with various social and economic complications, or they may contain more restrictive specifications of physical dependency and addiction, or psychological and physiological harm.[61, 130] Jellinek has described five different types of alcoholics which differ in degree and kind of psychological, behavioural and physiological involvement.[130] In some areas of North America, at least 2% to 5% of alcohol users become alcoholics and perhaps twice that many would be considered problem drinkers. The Addiction Research Foundation has estimated that in 1967 there were over 300,000 alcoholics in Canada.[1] The number is undoubtedly substantially higher today.

Only a small minority of alcoholics are 'down and out', 'skid row' variety derelicts; there are many alcohol-dependent persons in all levels of society who function in varying degrees of effectiveness in spite of their high alcohol consumption. Psychological and physiological disorders in these individuals vary considerably as a function of general life style and drinking patterns. Some heavy drinkers show little obvious functional impairment for long periods of time.

Some of the consequences of excessive alcohol use include increased physical and mental health problems, earlier death and a greater likelihood

of incarceration; discussion of these topics will follow directly. In addition, however, there are other consequences of alcohol use which involve not only the user, but others about him, and society in general.[138] A seemingly endless list of such consequences is possible, although those which are clear liabilities to society are the most frequently enumerated. As examples, heavy alcohol users are frequently cited as being responsible for injuring and killing large numbers of persons in automobile crashes and in acts of violence and aggression. Moreover, the legal handling, incarceration and rehabilitation of such individuals involve costs typically paid for by society as a whole. Alcoholics' increased accident rate adds to the costs of medical and automobile insurance, and their greater need for medical treatment decreases available hospital space and services already in short supply. They are more likely to create problems and misery for their families and their productivity while employed is frequently below par, partly due to their increased absenteeism.[210]

General Physical Health

The physical health of heavy alcohol users is typically poorer than that of the general population.[86, 156, 237, 252] Some illnesses result from the direct effects of alcohol, or they may involve other factors such as general life style, nutritional deficiencies, heavy use of other drugs (e.g., tobacco or Aspirin®), bodily injury due to accidents and other violent mishaps, inadequate hygiene and rest, over-exposure, overcrowding and other forms of stress.

Chronic heavy alcohol consumption often produces a loss of appetite for food and a disruption of normal digestion, absorption and, perhaps, utilization of essential nutrients. Heavy tobacco use, which is typical of alcoholics, often further reduces appetite. In addition, some alcohol-dependent persons choose to spend their limited funds on alcohol rather than adequately balanced meals. A large proportion of the diet of certain alcoholics is made up of alcoholic beverages (in some cases with weeks or even months with little else) and is thus dangerously low in protein, vitamins, minerals and other important food-stuffs. In addition to producing severe nutritional disorders, such diets may result in increased susceptibility to other diseases and infections.

Several liver diseases are related to heavy alcohol use. Cirrhosis of the liver involves a replacement of functional liver cells with scar tissue. Alcoholic liver cirrhosis is reported to develop after 10 to 15 years of heavy drinking and may lead to death.[292] Alcohol itself may be directly responsible for cirrhosis although other alcohol-related factors, particularly nutritional deficiencies, are typically most significant.[128, 161, 217] A Commission project examining societal factors influencing alcohol dependence in 45 countries replicated and extended the findings of others, showing that the incidence of cirrhosis in certain populations is positively correlated with *per capita* consumption of alcohol.[151, 230, 242, 258, 286] It has been estimated that 65–90% of the liver cirrhosis in certain parts of North America is attributable to heavy alcohol consumption.[7, 230] In the United States, alcohol prohibition brought

a marked decline in deaths due to liver cirrhosis, compared to the general mortality rates during the same period.[147] Cirrhosis fatalities rose gradually after prohibition was repealed and alcohol became freely available again. (See Figure A.1.)

Another serious liver impairment associated with alcohol dependence is alcoholic hepatitis; this illness involves inflammation of the liver with accompanying fever, abdominal pain and jaundice.[218] Other liver complications include a narrowing of the blood vessels serving the liver, and frequently, although apparently of lesser consequence, an increase in deposits of fat in the liver.[122, 160] Since many drugs are metabolized by the liver, alcohol-related liver damage may result in unusual or prolonged reactions to certain drugs in alcoholics, even when alcohol is not present in the body.

Heart disease is also seen in heavy alcohol users more frequently than in the general population. Although nutritional deficiencies and other factors can add complications, the cumulative effects of chronic alcohol consumption have been shown to impair the functioning of the heart and to result in metabolic and structural abnormalities before any difficulties are noticed by the drinker.[70, 232] The progression of the disease to produce heart failure, arrhythmias and other problems is not yet fully clarified, since a number of additional factors such as malnutrition, infections, excess trace metals sometimes found in beer, and the chronic use of other drugs such as tobacco may be involved.[193, 232] Heart disease has frequently been reported as a major cause of death among alcoholics.[148, 288]

Alcohol can also adversely influence other parts of the circulatory system. In one study blood cells were found to clump together forming a "sludge" in small vessels in the eye which slowed the rate of blood flow in proportion to the blood alcohol level; some vessels ruptured and others were completely blocked. The authors suggested that such effects may adversely affect many organs including the liver and brain.[194]

Gastrointestinal difficulties associated with heavy alcohol consumption include chronic gastritis, an undersupply of hydrochloric acid in the stomach, increased incidence of ulcers, and impaired absorption of various substances in the small intestine including thiamine, folic acid, xylose, fat and vitamin B_{12}.[184, 272] Heavy drinkers are also reported to have higher rates of cancer of the mouth, larynx, pharynx and esophagus; although heavy tobacco smoking is thought to add to the likelihood of some of these cancers, alcohol is also believed to be a significant factor.[66, 315, 316, 317] Various infectious diseases such as tuberculosis and pneumonia are also more frequently reported in heavy users of alcohol.[86]

Chronic and acute muscle disorders, involving muscle weakness, swelling, cramps and pain, have been related to heavy alcohol use. Both nutritional deficiencies and decreased oxygen to the muscles have been suggested as possible causes of these conditions.[167, 292] Other diseases associated with alcohol dependence, but due primarily to nutritional deficiencies, include pellagra,

FIGURE A.1

ALCOHOL PROHIBITION RELATED TO DEATH RATES FROM LIVER CIRRHOSIS AND FROM ALL CAUSES IN THE U.S.A.

Source: Klatskin, G. Alcohol and its relation to liver damage. *Gastroenterology*, 1961, 41: 445.

scurvy, anemia, brain damage and alcohol neuritis.[184, 292] Alcohol-related neurological disorders are discussed in more detail in a separate section below.

Regular, heavy alcohol use has significant effects on the secretion and metabolism of various hormones in the body, and some authors have suggested that many diseases of alcoholism are secondary to alcohol-induced disruption of endocrine function.[65] Disorders of the pancreas are frequently noted in alcoholics.[249] Low blood sugar and elevated fat content in the blood are also often seen.[184, 292]

The majority of the illnesses associated with heavy alcohol use improve when alcohol consumption is discontinued and diet and living conditions are improved. Frequently, recovery is near complete, although in some instances permanent damage or disability results.[156, 222] The general area of alcohol-related fatalities is discussed in more detail in a separate section below.

Adverse Psychological and Neurological Reactions

Heavy alcohol consumption is associated with a variety of psychiatric and neurological disorders. As with other drugs, it is often difficult to differentiate cause and effect in such correlations. Some investigators contend that only those individuals with serious psychiatric disorders become heavily involved in alcohol use, while others might argue from the same data that alcohol is primarily responsible for the pathology observed. In many cases it would appear that both factors are operating with considerable interaction.

In addition to the rather ambiguous but significant role of alcohol complications in various common psychiatric disorders, there are some relatively well defined organic conditions involving brain damage which are attributable directly or indirectly to the effects of chronic high-dose alcohol consumption. While the major psychiatric and neurological disorders associated with chronic alcoholism occur primarily in adults, there is considerable concern over the possible effects of heavy alcohol use on the maturation process in adolescents. Little adequately controlled research is available in this latter area, however.

The neurological complications of alcoholism are usually closely related to nutritional deficiencies which typically accompany chronic heavy alcohol consumption. Deficiencies in the vitamins thiamine, vitamin B_6, nicotinic acid and pantothenic acid are primarily responsible for such disorders of the nervous system,[156] although alcohol can have direct irreversible damaging effects on nerve tissue as well.

Some of the more serious alcohol-related neurological disorders include peripheral neuritis, Korsakoff's psychosis, Wernicke's syndrome, and Jolliffe's encephalopathy. Typical symptoms of alcoholic brain disorders include disorientation, clouding of consciousness, memory failure, hallucinations, rigidity of the limbs, and certain uncontrollable reflexes. Other frequently noted neuro-psychiatric conditions associated with alcohol dependence include

alcoholic hallucinosis, pathological intoxication, delerium tremens and various convulsive disorders or epilepsy complications.

The examination of hospital records provides some epidemiological information regarding the extent of alcohol-related psychiatric problems. As with other drugs however, the reliability and validity of psychiatric diagnoses associated with alcohol-related problems is often not adequate for survey purposes. In many cases, alcoholics may be hospitalized for treatment of their dependence rather than for other specific psychiatric disorders. In any event the number of alcohol-related cases must ultimately be interpreted in terms of the overall patient population, and more importantly, in terms of the extent and patterns of alcohol use in the general population from which the patients were drawn.

In the spring of 1971 the Commission conducted a national survey of the diagnostic records of psychiatric hospitals.[110] Although alcohol was of interest to the study, primary focus was on other drugs, and consequently, institutions specializing in the treatment of alcoholism were not included in the sample. Because of the frequency of serious non-neurological physical disorders associated with heavy alcohol consumption, many alcoholics are hospitalized in general hospitals rather than in psychiatric institutions. In spite of our *a priori* exclusion of the majority of alcoholism cases, alcohol was mentioned in the primary or secondary diagnoses of 5.1% of the psychiatric patients in the hospitals surveyed. This figure is three times that reported by the hospitals for all cases with other drug-related diagnoses combined. In British Columbia general hospitals with psychiatric wards were also surveyed. Alcohol was mentioned in the diagnoses of 41 (13.8%) of the 293 patients in the reporting hospitals.[d]

In the 1971 national mental health data published by Statistics Canada, alcoholic psychosis and alcoholism together accounted for 10,071 (17.5%) of the first admissions and 8,502 (16.5%) of the readmissions to psychiatric wards and institutions in the country.[34, e] The category of alcoholic psychosis includes delirium tremens, Korsakoff's psychosis, other alcoholic hallucinosis, alcoholic paranoia and other or unspecified alcoholic psychoses.[32] Alcoholic psychosis was diagnosed in 6.7% of the total alcohol cases. The alcoholism category includes episodic or habitual excessive drinking, alcohol addiction, and other or unspecified alcoholism. Overall, males outnumber females by a ratio of almost six to one in these cases. These data reflect a substantial increase in alcohol admissions from those reported in 1969. However, direct comparison among different years is hampered by the lack of consistency in the number of hospitals reporting from year to year.

Note that the Commission survey and the Statistics Canada data only include cases of alcohol complication of other psychiatric conditions when alcoholism *per se* is presented in the diagnosis. The total impact of alcohol on general neurological and psychiatric admissions is undoubtedly substantially greater than indicated in these data. (See also Tables A.5, A.6 and A.7 in the Annex to this appendix.)

Alcohol and Death

Heavy alcohol users as a group have been shown to have a higher mortality rate than persons of similar age in the general population. Studies in various countries have found that alcoholics are more likely than non-alcoholics to die from various accidents, poisoning with other drugs, suicide, homicide and certain diseases such as pneumonia, tuberculosis, liver cirrhosis, gastrointestinal ulcers, heart disorders and some cancers.[22, 45, 86, 100, 143, 163, 209, 241, 252, 277, 281, 304] Some of this literature has been discussed above.

In reports of violent death, it is often difficult to distinguish between acute or chronic effects of alcohol and various associated personality, social and life style factors. The nature of the relationship between alcohol and suicide is often not clear; alcohol use may be responsible for the suicidal state or in other cases heavy alcohol use might be the result of pre-existing emotional depression. The possible role of 'hangover' depression in suicide has not been clarified.

A study of alcoholics in Ontario found that suicide rates were six times the expected figure.[252] In another recent report from Ontario, approximately one-half of the males and one-quarter of the females who purposely injured themselves or attempted suicide were heavy drinkers.[134] Data from British Columbia indicates that alcohol was associated with more than one-quarter of all attempted suicides.[285] Similarly, in an investigation in the U.S. approximately one-quarter of suicide cases involved chronic alcoholics.[241]

The Federal Poison Control Program has reports of 651 ethanol poisonings or adverse reactions for 1971.[204] The majority of the poisonings occurred in persons over 25 years of age; approximately one-tenth involved children under 5 years of age. Males outnumbered females in these data by a little over two to one. It was not indicated whether these alcohol poisonings occurred singly or in combination with other drugs. Of those reports where the disposition of the case was specified, 38% resulted in hospitalization, with a median of 4–5 days institutional care. Of 67 drug death reports in which alcohol was mentioned, only 6 (9%) were attributed to alcohol alone; the remainder involved drug interactions, with alcohol and barbiturates being the most frequent fatal drug combination reported to the program. None of the alcohol-related deaths involved children.[f]

In the national statistics on *Causes of death*, published by the Federal Government, alcohol deaths may be coded under one of several different categories.[33] The following fatalities were reported for 1971:[m]

Alcoholism	350
Alcoholic psychosis (organic)	26
Alcoholic cirrhosis of the liver	739
Toxic effect (overdose)	10
Interaction with other drugs	204
Total	1,329

A little over two-thirds of these persons were males and the vast majority were over 40 years of age at the time of death. Alcohol-barbiturate combinations made up more than two-thirds of the drug interaction deaths.

For various reasons, these official mortality figures must be considered gross underestimates of the actual number of alcohol-related fatalities. Cases noted under the general category of alcoholism typically involve known alcoholics who died of some disease, such as pneumonia, heart attack, or gastrointestinal disorder, which was attributed to their chronic heavy alcohol consumption. The ascription of death to alcoholism or to another disease is often arbitrary, and apparently most alcoholic deaths are coded under various specific diseases rather than under alcoholism in death records.[40, 52, 100, 190, 252]

Canadian data suggest that approximately 65% of all liver cirrhosis deaths might be attributed to chronic heavy alcohol consumption in this country.[230] When this formula is applied to the total number of cirrhosis deaths reported for 1971, an estimate of 1,259 alcoholic cirrhosis fatalities is derived, which is almost double the number officially specified as such.[33]

The involvement of alcohol in overdose deaths associated with other drugs is apparently much greater than suggested by the above figures. For example, in a Commission study of coroners' reports of drug-related deaths, alcohol was found on autopsy in 44 (48%) of 92 opiate narcotic cases where toxicological findings were reported.[109] Death had been coded under opiates without mention of alcohol interaction in many instances.[81]

Dealing with fatalities among heavy alcohol users only, a 1971 report from the Addiction Research Foundation estimated that alcoholism in Canada contributed at least 6,000 deaths annually in excess of the expected mortality.[231] We have no accurate epidemiological information on the total number of deaths (among alcohol users and non-users) in Canada due to suicide, homicide or various accidents in which alcohol played a significant role. Existing data indicate that the number of such fatalities which could be attributed to the acute or chronic effects of alcohol would be substantial.

Alcohol and Crime[116]

Of all drugs used medically or non-medically, alcohol has the strongest and most consistent relationship to crime. In addition to over two and one-half million convictions for offences directly related to alcohol in Canada every year (including drunkenness offences; violations of the liquor control laws, such as operating stills, illegal importation and sales; and drunken and impaired driving) many other crimes are also related to alcohol use.[1, 224] However, many alcohol-associated criminal acts may not necessarily be attributable to the effects of the drug. For example, compared to non-delinquents, delinquents have been found to drink more frequently, and to report more solitary drinking, more drunken instances and less drinking with the family.[168, 223] Although drinking may be associated with crime in some such individuals, evidence suggests that alcohol is generally not the cause of

their delinquent behaviour. Instead, illegal alcohol use appears to be part of a general delinquent syndrome involving such acts as joy riding, vandalism, and malicious mischief.[16]

To some degree it is possible to predict future alcohol problems on the basis of earlier youthful delinquency. In one study 21% of the individuals who appeared at a psychiatric clinic as children were diagnosed alcoholic 30 years later, compared to only 3% of a group of matched control subjects. Forty-five per cent of the individuals with juvenile court records were subsequently diagnosed alcoholic.[238]

Alcohol use is frequently correlated with certain crimes in the chronic drunkenness offender or 'skid-row' alcoholic. Most of the offences committed by such persons are typically minor non-drug offences (such as vagrancy, trespassing and panhandling) which are often related to their lack of funds for food, shelter or more alcohol. Petty theft is an occasional charge, and it has been suggested that in order to "break into jail" temporarily for food and shelter, some individuals may commit some minor disturbance or crime against property.[72]

There is an abundance of evidence relating alcohol use to more serious crimes. Homicide is strongly correlated with alcohol use. In one frequently cited study in Philadelphia alcohol was present in either the offender or the victim in 64% of the homicides over a five-year period.[314] In 70% of the alcohol-related cases, alcohol was present in both the offender and the victim, while in only 17% and 14% of the cases had only the offender or the victim, respectively, been drinking. Murders were committed by stabbing, kicking, or beating by fists or with a blunt instrument in 70% of the cases, suggesting that serious alcohol-involved crimes tend to be unpremeditated, physical assault. A study of coroners' cases in Victoria found that out of 41 murder victims tested for alcohol, 19 had a blood alcohol level of over 0.15%.[19] A Canadian study of ex-prisoners concluded that an abnormally high proportion of excessive drinkers had committed crimes against the person, and a lower proportion had committed crimes against property. Excessive drinkers also had a higher proportion of sex crimes.[53] A strong relationship between alcohol use and sex crimes such as rape and incest has been demonstrated in many other studies around the world.[4, 8, 228, 236]

A study of drinking was made in 415 self-referred and 260 court-referred patients to the Winnipeg Psychopathic Hospital between 1956 and 1959.[219] Drinking histories were as follows:

	Court-referred Patients (N 260)	*Self-referred Patients (N 415)*
Abstainers	8%	44%
Moderate drinkers	17%	22%
Problem drinkers	40%	11%
Alcoholics	35%	22%

A significantly higher percentage of the psychiatric patients who had been in trouble with the law had drinking problems. Of the court-referred patients, 55 were charged with sex offences, and of these, 54% were problem drinkers and 22% were alcoholics. Homicide was contemplated, attempted or committed by 42 of the court-referred patients, and 95% of these were problem drinkers. Seventy-three per cent of these individuals were intoxicated at the time of the offence. Of 43 patients who had committed theft or forgeries, 70% were problem drinkers.

Persons with alcohol problems constitute a considerable proportion of people imprisoned in Canada for serious offences. Of a total of 4,057 males who were committed to penitentiaries for such offences in 1969, 1,053 (20%) were judged to be problem drinkers and 360 (9%) were alcoholics, making a total of 29% of the admitted male inmates with serious identified drinking problems. Of some selected crimes, alcoholics and problem drinkers were involved in 33% of the murders, 38% of attempted murders, 54% of manslaughters, 39% of rapes, 42% of other sexual offences, and 61% of assaults. Of female admissions for serious crimes, 16 (22%) out of a total of 72 were judged to be problem drinkers.[31]

Tolerance and Dependence

Tolerance to most of the immediate effects of alcohol develops with frequent heavy use, although it does not occur as rapidly or to the same degree as with opiate narcotics. For example, tolerance to the lethal effects of morphine may be in the order of 25- to 100- fold, while tolerance to the lethal dose of alcohol may only be doubled under comparable dependence conditions.[259] Alcohol is more like the barbiturates and other sedative hypnotics in that limited or "incomplete" tolerance develops.[114, 139] The rate of acquisition and extent of tolerance depends on the pattern of use. Regular heavy drinkers may be able to consume two or three times as much alcohol as a novice. In Western culture, some symbolic masculinity frequently accompanies the development of tolerance and the ability to 'hold one's liquor'.

Most intermittent or moderate drinkers show little tendency to increase dose, although regular heavy drinkers may, in order to obtain the desired psychological effects, ingest quantities which lead to symptoms of chronic alcohol toxicity. A decrease in the sensitivity of the nervous system to alcohol is probably more important than metabolic mechanisms in the development of tolerance.[139] Learning to function under the influence of alcohol may further reduce some of the acute behavioural effects of intoxication in regular users. As noted above, relatively little tolerance develops to the lethal dose, and acute alcohol poisoning is sometimes noted as a cause of death in alcoholics, although nausea, vomiting and unconsciousness usually prevent self-administration of a fatal overdose. In some alcoholics, tolerance later

seems to decline and a special response or oversensitivity to certain effects of alcohol (pathological intoxication) may develop. In such individuals even a single drink may produce profound loss of control and initiate unrestricted further indulgence. Alcohol-related liver damage may play a role in such phenomena.

Physical dependence on alcohol occurs with the development of tolerance in some long-term heavy drinkers. Although alcoholic hallucinosis, delirium tremens ('DT's'), and convulsions ('rum fits') were noted and studied in the 19th century, only relatively recently was it demonstrated that these symptoms are essentially part of the physical dependence withdrawal syndrome.

Isbell and Mendelson and their associates have clearly demonstrated that even when diet is controlled, a characteristic severe withdrawal syndrome can occur in individuals who had been heavy drinkers, after only a few weeks of continual drinking of large doses of alcohol.[121, 180] The quantities of alcohol ingested in these studies were considerably greater than those normally consumed. With the usual drinking patterns overt physical dependence may not appear until after years of heavy consumption. Some problem drinkers seem never to become physically dependent on alcohol.[130]

The overall picture of the alcohol abstinence or withdrawal syndrome is generally similar to that associated with barbiturate dependence. As with other drugs, the number and severity of the withdrawal symptoms varies with the quantity of the drug regularly consumed before use was stopped. The abstinence syndrome typically involves loss of appetite, nausea, anxiety, sleeplessness, severe agitation and irritability, confusion, tremors, sweating and, later, cramps, vomiting, illusions and hallucinations. In severe cases, after several days delirium tremens develops and convulsions, exhaustion and cardiovascular collapse may occur. The delirium tremens stage occurs in about 5% of withdrawal cases.[175] Although reports are inconsistent, death may result in 10% of those undergoing severe withdrawal without treatment.[6] Major recovery in those surviving usually occurs within a week, although certain symptoms continue for a much longer period.[139, 298] The full blown alcohol or barbiturate type withdrawal syndrome is considerably more dangerous than that of the morphine type, which is rarely if ever fatal.

Psychological dependence on alcohol occurs in many individuals and such dependence is often accepted and tolerated in contemporary North America. A great number of people regularly turn to alcohol for relief or aid prior to or after facing a stressful situation, to escape worries, troubles or boredom, to relax and enjoy a party, or even to sleep, and many feel they do not function as well in certain situations without a drink or two. There is a strong psychological component in the drinking behaviour of the developing alcoholic as his drinking becomes more and more compulsive in spite of the obvious consequences.

Alcohol and Other Drugs

Pharmacological Interaction

The psychological, physiological and biochemical effects of alcohol can be modified by the presence of other drugs; likewise, alcohol can influence the effects of many other substances. Although research regarding drug interactions has been considerably less extensive than that involving the effects of single drugs, knowledge in this important area is increasing at a rapid rate. Because of the prevalance of alcohol consumption in our society, the interaction of alcohol with other drugs used medically and non-medically is of considerable significance.[76, 78, 292] The preparation of this summary was greatly facilitated by the annotated bibliography on alcohol interactions prepared by Eric Polacsek and associates of the Addiction Research Foundation.[221]

Barbiturates. The combination of alcohol and barbiturates may result in effects which are greater and longer lasting than that produced by either drug alone. Under certain conditions sedation is potentiated, resulting in a greater effect than that expected by simply adding the reactions produced by each drug when administered alone. Toxic reactions and death can result from doses of alcohol and barbiturate in combination which, administered singly, are well below the lethal range.[60, 71, 133, 169] The mechanisms for these effects are not yet fully understood, but it has been found that the presence of alcohol in the body can decrease the rate of barbiturate metabolism.[192]

Alcohol and barbiturates also demonstrate cross-tolerance; it has long been recognized that regular heavy users of alcohol have a diminished response to barbiturates, and vice versa. This cross-tolerance appears to be primarily due to changes in the responsiveness of the brain following regular heavy use of either drug.[114, 139, 192] Thus, heavy alcohol users are less sensitive to barbiturates when taken alone, but become increasingly responsive after consuming alcohol. The development of cross-tolerance does not appear to significantly affect the lethal dose, and large quantities of alcohol and barbiturates taken simultaneously may produce a toxic or fatal reaction, even in individuals with high tolerance to other effects. Alcohol and barbiturates also show a considerable degree of cross-dependence, and barbiturates are frequently used therapeutically to reduce the severity of withdrawal in persons physically dependent on alcohol.

Non-barbiturate sedatives and minor tranquilizers. Alcohol combined with certain non-barbiturate sedatives and minor tranquilizers may, under certain circumstances, produce a more intense and prolonged sedation than is produced by either drug alone, although the literature is not consistent in this respect. In only a few studies have such combinations resulted in a potentiation of effects. Minor tranquilizers such as chlordiazepoxide (Librium®), diazepam (Valium®) and meprobamate (Equanil®) did not increase the sedation produced by alcohol in some investigations.[38, 60, 78, 140]

Cross-tolerance and cross-dependence have been demonstrated between alcohol and some non-barbiturate sedatives and minor tranquilizers.

Since the minor tranquilizers are frequently used by non-hospitalized patients, some of whom are likely to drink alcohol and drive automobiles, there has been considerable interest in evaluating the effects that these drug combinations might have on skills related to driving. Such interaction studies have included only limited measures of psychomotor, intellectual and perceptual functions, but the results are generally comparable to those investigating general sedation: enhanced impairment has been found with some substances, no effects with others, and, under some conditions, certain of these drugs may reduce the response to alcohol.[38, 39, 79, 88, 140, 153, 185, 199, 319] Similarly complex interaction may be expected for combinations of alcohol, and certain antihistamine and anticholinergic drugs. Many such substances are available and relatively little human research has been done in this regard.[62, 117, 265, 300]

Volatile solvents. Volatile solvents are sometimes taken in conjunction with alcohol by certain individuals, who report that some of the subjective effects produced by these drugs are thereby enhanced. Also, alcohol has been shown to augment the adverse effects of the volatile anesthetic, trichloroethylene, on visual-motor performance.[68] Furthermore, cross-tolerance between alcohol and solvents has been suggested by the frequently reported insensitivity of chronic alcohol users to ether anesthesia.[104]

Major tranquilizers. Numerous studies suggest that many of the major tranquilizers, including phenothiazines, thiozanthines, butyrophenones and rauwolfia alkaloids (all of which are used primarily in the treatment of psychosis) may produce an increase in sedation when taken concomitantly with alcohol.[50, 191] Since many patients receive such medication on an outpatient basis, some researchers have expressed concern regarding automobile driving and social interactions if alcohol is taken concomitantly.[149, 218]

Anti-depressants. Certain drugs used to treat severe depression (especially the monoamine oxidase inhibitors such as Parnate®) may exaggerate the toxic effects of alcohol and vice versa when the drugs are taken together. The mechanism of such effects is uncertain. Some other anti-depressants, such as imipramine (Trofranil®) and amitriptyline (Elavil®) may also alter the effects of alcohol, but the interaction is not as consistent or pronounced as with the former class of compounds.[78, 118]

Opiate narcotics. Surprisingly little human research has been done regarding the interaction of alcohol and the opiate narcotics, such as codeine, morphine, heroin and methadone. On the basis of evidence obtained in animal experiments and from studies of death due to overdose of opiate narcotics and alcohol in humans, it is clear that the dose of either of these drugs which produces sedation, toxicity and death is substantially lower when they are used together.[62, 63, 203, 301]

Alcohol does not exhibit significant cross-tolerance or cross-dependence with the opiate narcotics. However, opiate narcotics can reduce or mask some of the symptoms of alcohol withdrawal or 'hangover'. There is almost no evidence regarding other potentially important psychological and physiological interactions resulting from opiate narcotic and alcohol combinations in humans. This is clearly a high priority research area.

Stimulants. The results of research regarding the interaction of alcohol and stimulants such as caffeine and amphetamine are, in general, complex, conflicting, and incomplete, but it does appear that some of the sedative effects of alcohol can be reduced by certain stimulants. Amphetamines have been reported to reverse the impairment due to alcohol on some, but not all tests involving mental addition and the learning of new material.[282, 311] In another investigation, amphetamines overcame alcohol-induced changes in certain minor involuntary eye movements.[11] However, in a series of studies involving motor skills and verbal performance under stress, amphetamines did not antagonize the detrimental effects of alcohol even when the subjects were fatigued.[117, 141] Amphetamines have been reported to reduce the gross behavioural signs of alcohol intoxication in alcoholics and to decrease some of the symptoms of 'hangover'.[23, 186, 235]

Some researchers, but not all, contend that caffeine decreases certain symptoms resulting from high doses of alcohol, including potentially fatal depression of respiration.[78, 237] With moderate doses of caffeine there may be some transient improvement in feelings of alertness, but caffeine has not been shown to improve psychomotor coordination impaired by alcohol.[77] Smoking tobacco in combination with alcohol or with alcohol and coffee may enhance the detrimental effects of alcohol on psychomotor coordination.[124, 208, 215]

Cannabis and hallucinogens. The interaction between alcohol and cannabis has only recently begun to be systematically explored. Cannabis increases certain alcohol effects on behaviour in mice,[73, 97] but apparently does not affect the lethal toxicity of alcohol.[69] It has been shown in Commission research and in studies of another group that cannabis and alcohol can have additive effects on certain psychomotor and physiological functions, and that marijuana may intensify the sedative properties of alcohol under some conditions.[172, 173, 189, 233] On the other hand, the two drugs may have antagonistic effects on some subjective variables such as visual imagery.[233] In the Commission study, cannabis altered the alcohol effects without changing the rate of alcohol metabolism or disappearance from the blood (as measured by the *Breathalyzer*).

Alcohol interactions with LSD and related drugs have not been systematically explored, but antagonism of certain effects has been reported by illicit users. Alcohol enhancement of the sedative properties of PCP is to be expected.

Non-psychotropic drugs and antagonists. Alcohol may also interact with a number of drugs which have little or no psychotropic effect, or are

rarely used for such purposes. Of primary interest here are substances which may reduce or eliminate the acute effects of alcohol, post-intoxication hangover, or withdrawal symptoms in alcohol-dependent persons. Some other drugs used in conjunction with the medical management of alcoholism are discussed as well.

A substance which could reverse the short-term effects of alcohol would be of considerable practical importance in both medical and social contexts. Unfortunately, at present there is no known pure alcohol antagonist, although a number of substances have been shown to reduce some of the acute effects of alcohol. One report noted that multiple vitamins (B_1, riboflavin, pyridoxine and calcium) can reduce alcohol subjective effects and impairment of reaction time.[142] Diarginine ketoglutarate has been reported to lower blood alcohol levels after drinking, and to reduce alcohol effects on certain psychological and physiological measures.[44] In one study carbamazepine almost entirely compensated for errors caused by alcohol in a visual field test.[257] Intravenous infusions of fructose (a sugar obtained from fruit sources) have recently been reported to increase the rate of alcohol elimination in alcoholics by 25%, thereby presumably resulting in quicker recovery.[24] Antacids taken during or after drinking reduce nausea and other gastrointestinal symptoms of alcohol intoxication and hangover.[96]

Mendelson and associates[181] recently reported that alcoholics who were given propranolol displayed smaller alcohol-induced decrements in performance than control subjects on assessments of reaction time, hand steadiness, manual dexterity, flexibility of attention, and ability to change perceptual motor sets. Alcohol-induced mood change was reduced as well. The antagonism of alcohol effects in this study was small but consistent. In addition, propranolol has been used to reduce mild alcohol withdrawal symptoms such as trembling, nausea, stomach cramps, and vomiting, and to temporarily reduce craving for alcohol.[269] Apomorphine has also been shown to at least temporarily decrease craving for alcohol.[250]

Disulfiram (Antabuse®) and calcium carbimide (Temposil®) are often used to encourage abstinence in alcoholism therapy. Antabuse® was developed in Denmark in the late 1940s[102] and Temposil® in Canada in the early 1950s.[67] Both drugs alter the process by which the body metabolizes alcohol, but have little other relevant pharmacological activity. They are sometimes mistakenly discussed as alcohol antagonists. Under normal drinking circumstances ethyl alcohol breaks down into acetaldehyde when it is oxidized in the body. Acetaldehyde is highly toxic but is usually destroyed so quickly that its effects are minimal and rarely noticed. But with the introduction of disulfiram or calcium carbimide, the metabolism of the acetaldehyde is retarded so that intensely unpleasant effects occur (called the acetaldehyde syndrome) which may include nausea and vomiting (and, in severe cases, dangerous cardiovascular effects). A patient given maintenance doses of disulfiram, for example, can not use alcohol without becoming immediately sick.[103] In order to provide a long-lasting deterrent to drinking, long-acting implantable disul-

firam preparations have been developed which are effective for six to eight months. In one study, 20 of 22 patients achieved total abstinence over a period of 8 months after such treatment, while 11 of 12 non-implant patients returned to drinking within two months following discharge.[120] Further research with such implants is clearly warranted.

Patterns of Multiple Drug Use

Alcohol is currently used by the majority of the Canadian population. Most of these individuals also use other psychotropic drugs non-medically, with caffeine and nicotine being most frequently mentioned. Heavy users of alcohol are almost invariably heavy tobacco smokers and as noted earlier, this high correlation is a frequent complicating factor in interpreting studies of the physical effects of alcohol.

In general, alcohol users are more likely than abstainers to be users of barbiturates, tranquilizers, opiate narcotics, volatile solvents, amphetamines, cannabis and other hallucinogens, and a variety of other prescription and non-prescription drugs. (See Appendix C *Extent and Patterns of Drug Use.*) Alcoholics are frequently heavy users of other sedative-hypnotics such as barbiturates and minor tranquilizers.[56, 57] Likewise, heavy users of barbiturates, minor tranquilizers and opiate narcotics generally turn to alcohol if the supply of the preferred drug is restricted. Most opiate narcotic-dependent persons have histories of heavy illicit alcohol use as adolescents.[240, 275] Alcoholism is one of the most serious problems regularly associated with opiate narcotic dependence, and heavy alcohol consumption is common among many former heroin users and patients in methadone maintenance programs.[83, 100, 293]

The relationship between cannabis and alcohol use has been the subject of much controversy. Some have suggested that cannabis may be a cure for society's alcohol ills. In general, survey studies indicate that those who use alcohol are much more likely than 'teetotallers' to use cannabis, and that most cannabis users still drink alcohol. In addition, heavy users of cannabis tend to drink more alcohol than light or infrequent users.[12, 15, 27, 94, 150, 170, 216, 271, 273, 290] However, in a recent survey in Toronto, heavy users of alcohol used less cannabis than more moderate drinkers.[272] In a retrospective study of black males in St. Louis, a higher incidence of alcoholism and related problems was found among cannabis users than non-users.[239] However, we have no information from most of these studies as to the effect cannabis had on an individual's drinking behaviour and overall alcohol intake.

Many researchers have mistakenly assumed that cross-sectional survey data indicating a positive *between-subject* correlation of cannabis and alcohol use, at a single point in time, implies a positive relationship between the use of the two drugs within an individual over time, which is the relationship of ultimate interest. This extrapolation is unjustified logically and statistically.[41] Evidence of an association (either positive or negative) between the

use of two drugs in a population at a given time provides little information as to the relationship (if any) between the levels of use of the drugs within the individual members of the group. Changes in behaviour over time, within an individual, must be studied directly. Even then, other secondary data in addition to drug use patterns must be considered in order to determine causal factors.

The bulk of the limited retrospective *within-subject* data now available suggest that cannabis use may reduce or interchange with alcohol consumption to some extent in the user population. In many surveys, including several Commission studies, a substantial proportion of cannabis users claimed that they have significantly reduced their consumption of alcohol or quit it since using cannabis.[94, 95, 99, 101, 150, 179, 214, 267, 318] There is a reported tendency, with cannabis use, for a greater reduction in the use of hard liquor than of the milder forms of alcohol. The combined consumption of cannabis with wine or beer is common in some social circles. Anecdotally, in certain parts of the United States, alcohol sales in university areas reportedly declined as marijuana use increased, in spite of generally spiralling alcohol sales across the country.[207] Also of interest, five fraternities on a mid-western U.S. campus reported that the proportion of social funds spent annually on alcohol had been reduced considerably since marijuana use became common. No indication of alcohol abstinence appeared in these fraternities, however.[187] None of these reports present definite, verifiable evidence of a reduction in alcohol use, so conclusions must be guarded.

Some cannabis users claim that alcohol effects dominate and, for that reason, they refuse to mix the drugs even if they enjoy each one separately. However, in several studies, including Commission experiments, where alcohol and cannabis were given separately or together in low doses under 'blind' conditions, some experienced cannabis users were not particularly proficient at identifying the predominant drug action.[105, 135, 233] Differentiation is easier at higher doses, however, and alcohol does appear to reduce some of the psychedelic aspects of cannabis.[55, 233]

Comparing the benefits and harms of alcohol and cannabis has become a popular and engaging activity. Due to the profoundly different social connotations, patterns of use, and scientific knowledge of these drugs, such a comparison must be made on limited and tenuous grounds. As discussed in the Commission's *Cannabis Report*, only a few experiments have been done comparing cannabis and alcohol in humans.[28, 198] Two such studies were conducted by the Commission.[105, 189, 233]

It would appear that individuals who actually quit alcohol use because of cannabis constitute a minority of users, and their choice of drugs may have more to do with their particular value systems than with the pharmacological properties of the drugs. The hostile attitude towards alcohol expressed in the past by some cannabis-using youth is clearly not reflected in the majority of cannabis users today. Combined use is becoming increasingly common.[83] Systematic prospective studies have not been done, and it is not

clear from the data whether, on a large scale, cannabis would tend to replace alcohol as an intoxicant in the user population, or whether the use of these drugs would be additive without significant interaction, or if the use of one might potentiate or increase the consumption of the other. As measured separately, the use of alcohol and cannabis are both increasing in Canada, especially among young people.[150, 272] (See also Appendix C *Extent and Patterns of Drug Use* for further discussion of multiple drug use.)

A.7 BARBITURATES

Introduction

The term 'barbiturate' refers to drugs which are derivatives of barbituric acid (malonylurea). Barbituric acid itself has no significant psychotropic properties, but its derivatives may have a variety of effects on the central nervous system. Certain of those compounds with significant depressant or sedative-hypnotic properties are of primary importance in medical and non-medical use. Many of the short-term subjective effects of the barbiturates are remarkably similar to those of alcohol.

The first drug of this class to be synthesized, barbital (also called barbitone or Veronal®) was introduced to medicine in Germany in 1903.[134] Barbiturates rapidly gained a common usage as tranquilizers, sedatives, hypnotics (sleep inducers) and anesthetics, and today are considered indispensible to medical practice. In the past decade, however, the preference for barbiturates in some medical applications has declined, primarily due to the availability of other drugs with certain similar effects, including the minor tranquilizers (such as Valium®, Librium® or Equanil®). The minor tranquilizers and other non-barbiturate sedative-hypnotics are discussed in Appendix A.8 which follows. Although significant differences exist in some instances, the general pharmacological similarities between the barbiturates and many of these other drugs are such that these substances are often considered together as a group under the heading of "anxiolytic sedatives".[100, 169] In 1971, barbiturates were estimated to account for more than one-fifth of all prescriptions for mood-modifying drugs in Canada, and are second only to the minor tranquilizers in total prescriptions in both Canada and the United States.[18, 157]

Although some problems with non-medical barbiturate use were noted soon after these drugs were introduced, in the 1930s there was considerable controversy regarding the nature and extent of chronic barbiturate intoxication and the consequences of their non-medical consumption.[50, 59, 167] The significance of barbiturate dependence and its similarity to alcoholism and, to a lesser degree, opiate narcotic dependence has become apparent only in the past few decades.[42, 50, 76] For many years, barbiturates have been the leading toxic agents involved in fatal poisonings and suicides in North America.

In the past three-quarters of a century, an estimated 2,500 different pharmacologically active derivatives of barbituric acid have been developed, of which perhaps 25 to 50 have been marketed for medical use.[50, 134, 156] Less than a dozen make up the bulk of current use in Canada. The barbiturates vary in the potency, latency and duration of their effects, but there is considerable overlap among them and differences are generally only a matter of degree. They are often classified by the duration of their sedative or hypnotic action at a standard dose.

Among the most widely used barbiturates in Canada are the short- to intermediate-acting compounds, including amobarbital (Amytal®), secobarbital (Seconal® or 'reds'), pentobarbital (Nembutal® or 'yellows') and butabarbital (Butisol®). Tuinal®, a mixture of amobarbital and secobarbital, is very popular in both medical and non-medical use. Similar barbiturates which have been singled out as likely candidates for non-medical use in the United States include cyclobarbital, heptabarbital, probarbital, talbutal and vinbarbital.[156] Long-acting barbiturates, such as phenobarbital (Luminal®) and the ultra-short-acting variety, such as hexobarbital (Evipal®) or thiopental (Pentothal®) are commonly employed for medical purposes, but are less often used non-medically than are the intermediate compounds.

In North America it has been traditional to use names ending in "al" for the barbiturates; in Great Britain the letters "one" are commonly suffixed instead (e.g., barbital or barbitone). In addition to descriptive slang terms based on the usual colour of the pharmaceutical capsule (e.g., 'reds', 'yellows', 'blues', 'rainbows', etc.), barbiturates are often referred to as 'sleeping pills', 'barbs', 'downers', or 'goof balls'.

It is frequently said that in North America the supply of barbiturates lawfully manufactured or imported greatly exceeds the requirements of legitimate medical use or exportation.[18, 156, 157] Many current non-medical users were initiated into barbiturate use under medical auspices; such persons may develop dependence and maintain use long after the original medical rationale for the prescription is absent. Apparently most of these barbiturate users continue to obtain the drugs through legitimate channels.[63] Since many physicians do not adequately maintain or monitor prescription records, a patient may be able to arrange an increase in the frequency and/or quantity of drug prescribed. In addition, many chronic users of barbiturates and other prescription drugs obtain 'legitimate' prescriptions from a number of different doctors simultaneously, without the physicians' awareness.[65] (See also Appendix B.7 *Sources and Distribution of Minor Tranquilizers, Barbiturates and Other Sedative-Hypnotics.*)

The occasional medical and non-medical use of barbiturates appears to be widespread across age groups and social classes, but the chronic use of these drugs has seemed to be most common among persons over 30 years of age. Prescription controls are only partially effective; possession of these drugs for personal use without medical authorization is not a criminal offence;

and users do not appear to form a homogeneous, cohesive or easily recognized minority. Hence, the usual medical and legal data sources and other traditional research techniques have been of relatively little assistance in assessing the extent and consequences of non-medical barbiturate use in Canada. While a considerable body of research exists into the many medical applications of these drugs, there has been relatively little systematic investigation of non-medical use. As with other drugs which are widely available on a prescription basis, the distinction between the medical and non-medical use of barbiturates is often particularly difficult to make. An increase in the extent of barbiturate use among young people in the United States has recently become the focus of much attention.[156, 157] In Canada, there are some indications that the use of these drugs by teenagers and young adults may be growing as well.[61] (See also Appendix C *Extent and Patterns of Drug Use.*)

Medical Use

The medical uses of barbiturates are based on their sedative, hypnotic, or anti-convulsant effects. In low doses (e.g., 25–50 mg), the short- or intermediate-acting compounds are widely used as sedatives or tranquilizers in the treatment of tension and anxiety. The hypnotic effect of these drugs is familiar to thousands of Canadians who use barbiturates in higher doses (e.g., 100–200 mg) in the form of the common sleeping pill. Barbiturates are regularly administered as anesthetics or pre-anesthetics (often in conjunction with other drugs) in surgical or dental situations; but they have little effect on pain if used alone.[68, 125] The ultra-short-acting compounds are most commonly used as intravenous anesthetics. The anti-convulsant effects of certain barbiturates have been very important in the treatment or prevention of acute convulsions associated with tetanus, various neurological disorders including epilepsy, poisoning due to the overdose of stimulants such as strichnine, nicotine or cocaine, and withdrawal symptoms associated with alcoholism and other sedative drug dependence. The intermediate- to long-acting barbiturates are those most commonly employed in anti-convulsant applications. The convulsion-blocking properties of these drugs are not necessarily correlated with their general sedative potential. Barbiturates have also been employed in the treatment of asthma, pre-menstrual tension, motion sickness, nausea and vomiting, peptic ulcer and other gastrointestinal disturbances, hyperthyroidism, and high blood pressure and other cardiovascular disorders.[100, 106, 134] Barbiturates may be used to treat adverse reactions or 'bad trips' associated with LSD and other hallucinogenic drugs.

Occasionally barbiturates may assist in the diagnosis and psychotherapy of certain psychiatric disorders. In some applications the drug is administered in a slow intravenous infusion with the dose adjusted to keep the patient in a semi-conscious state, relaxed and uninhibited, thereby facilitating communication, diagnosis and perhaps therapy. This procedure is essentially the same

as that used in the so-called 'truth serum' application in criminal investigations. This latter effect is just a carefully monitored response to common barbiturates. While this procedure frequently results in information which is less inhibited or otherwise different than that normally communicated, there is little evidence that it actually exposes the 'truth' as such.

As noted earlier, the use of barbiturates as day-time sedatives, tranquilizers and sleep inducers has declined somewhat in the last decade due to the increasing popularity of certain minor tranquilizers and non-barbiturate sedatives, some of which are considerably less physically toxic than the barbiturates. Heavy sedation of psychotic patients with barbiturates was once common in certain psychiatric hospitals, but these drugs have been largely replaced in such applications by the major tranquilizers or neuroleptics (such as the phenothiazines) which can control many symptoms of psychosis without extensive depression of central nervous system functioning.

In summary, the barbiturates are considered indispensible in certain aspects of medical practice, but in many common prescription applications they could be replaced by other drugs which are less likely to produce significant adverse effects as a result of non-medical use.

Chemical Analysis of Illicit Samples in Canada

There has been surprisingly little systematic chemical analysis of illicit barbiturates in Canada. These drugs were not specifically mentioned by Marshman and Gibbins in their summary discussion of illicit drug samples analysed at the Addiction Research Foundation of Ontario in 1969–70.[105] The Health Protection Branch quantitative analysis study of police seizures does not include barbiturates as primary drugs for special analysis, nor were any found mixed with the opiate narcotic, amphetamine or hallucinogen samples reported by HPB to the Commission for 1971–72.[62,b] The HPB has identified 339 barbiturate samples among the total police seizures for the 12-month period ending in March 1973.

In the Commission's study of illicit drug samples (1971–72) no barbiturates had been presented to the researchers as such.[114] However, barbiturates were detected in 28 (2.9%) of the 980 drug samples analysed. Eight samples were reported to contain only barbiturates; these had been represented as LSD, 'speed' or were of unspecified identity. Ten samples contained barbiturates in combination with methamphetamine and nine with LSD. These samples had generally been presented as methamphetamine or LSD respectively.[c]

These data suggest that barbiturates were not a major item in that part of the illicit drug distribution system assessed by these studies (i.e., primarily the youth-oriented market). It appears that the samples that were found came originally from legal sources; there were no indications of illicitly manufactured barbiturates. (See also Appendix B.7 *Sources and Distribution of Minor Transquilizers, Barbiturates, and Other Sedative-Hypnotics.*)

Administration, Absorption, Distribution and Physiological Fate

In crystalline form, barbiturates are odourless white or yellow powders with a slightly bitter taste. They are available as powders, elixirs, injectable solutions, suppositories, capsules or tablets (in both sustained and delayed release forms). Barbiturates are frequently marketed for medical use in mixtures with other drugs such as other sedatives, tranquilizers, analgesics, belladonna alkaloids (atropine or scopolamine), various stimulants (amphetamine or caffeine), vitamins and certain gastrointestinal therapeutic agents.[132]

Barbiturates are usually administered orally for both medical and non-medical purposes, and are readily and efficiently absorbed by the stomach, small intestine, and rectum.[106, 134] After ingestion, absorption is most rapid on an empty stomach, and effects of some barbiturates may occur within 20 minutes. A full stomach may double the time required for effective absorption. Both intramuscular and intravenous injections are efficient, but they are prone to physical complications and are generally avoided except for special purposes. Barbiturates are almost never given subcutaneously since they can cause considerable local pain under the skin and may seriously damage the tissue. Persons who inject barbiturates non-medically usually prepare a solution of tap water and crushed tablets or capsules originally intended for oral use.

After absorption into the blood stream, barbiturates are distributed rather uniformly throughout the body, but the various barbiturates show some individual differences in the facility with which they enter the brain. These drugs readily cross the placental barrier into the fetus in pregnant women. Barbiturates are eliminated by the kidney in the urine, partly in their original form, but largely as breakdown products resulting from enzymatic metabolism in the liver. Metabolism is more extensive and subsequent excretion is faster with the shorter-acting barbiturates. Binding of the drug in the blood plasma or by tissue protein, and its affinity for tissue fat may also affect the rate at which the barbiturate is eliminated from the body and its net effect on the nervous system. The short-acting barbiturates are highly lipid soluble and may accumulate in body fats with repeated use. Variations in distribution, metabolism and excretion are largely responsible for the differences in potency, latency and duration of action of the different barbiturates.[13, 85, 134]

Barbiturates stimulate the production of the enzymes responsible for their metabolism in the liver, thus resulting in more rapid and efficient deactivation and a shorter duration of action with repeated use. Since many drugs are metabolized by the same non-specific enzyme systems, barbiturate use may alter the body's response to other substances as well. Liver diseases or damage, such as those associated with chronic heavy alcohol use, reduce the rate of barbiturate metabolism and subsequent excretion, and may result in an exaggerated or extended response.[23, 26, 85]

Barbiturates and their metabolites are readily detectable in body fluids using standard analytic methods.[5, 21, 38, 83, 148] However, the quantity of fluid and the time required for extensive analysis using traditional techniques reduces the usefulness of the methods in certain applications. Recently, radio and spin immunoassay techniques have been described which allow a rapid, specific and extremely sensitive analysis of minute samples.[101, 143]

Psychological Effects

The short-term psychological and behavioural effects of barbiturates are highly similar to those of alcohol. Depending on the conditions of use, at low doses barbiturates typically result in relaxation, a heightened sense of well-being, and often drowsiness and a moderate decrease in alertness and attention. Alternatively, the same dose may produce a period of excitement during which the individual is more sociable, jovial, impulsive, or energetic. There may be decreased inhibition of certain drives and, depending on the individual, one might feel more amorous, aggressive, creative, playful or hungry.

At higher doses, the effects of the drug on the motor system become apparent, and include a diminished ability to react quickly and to perform skilled precise tasks. Sedation is common. The emotions are often labile, and the individual may alternate between feelings and displays of unusual affection, euphoria, or hilarity, on the one hand, and rudeness, hostility, aggressiveness and violence, on the other. Emotional depression, self-pity and social withdrawal are not uncommon. (The involvement of barbiturates in suicide is discussed below.) At still higher doses slurred speech, blurred vision and an unsteady gait occur along with other signs of drunkenness. The individual may have difficulty walking or manouvering around simple obstacles without collisions or falls, and there is characteristic confusion and difficulty communicating effectively. With such doses, behavioural sedation often becomes predominant and the individual may fall into a stupor or sleep. Intravenous barbiturate use may produce a 'warm rush', but not the 'flash' or 'splash' associated with cocaine or methamphetamine injection.

The variability in the short-term response under medically supervised conditions is described by Wikler:

> After intravenous injection of 0.25 to 1.0 gm of amobarbital, a subject may fall asleep if he lies in bed undisturbed, yet he may be awake and voluble if interviewed by a psychiatrist, or he may exhibit ataxia on attempting to walk back to his bed, but he may 'sober up' promptly when instructed to pose for a motion picture demonstration of ataxia.[160]

Driving

Several reviews of the drugs and driving literature in Canada and the United States have concluded that there is little evidence that barbiturates have contributed significantly to highway crashes.[90, 119, 138, 160] In Canada,

arrests for impaired driving involving barbiturates are rare, perhaps in part because the use of these drugs is not detectable with a *Breathalyzer* or other convenient test, nor do they produce any characteristic odour on the breath. Recently, an increase in driver and pedestrian arrests involving barbiturate use has been reported in some areas of the United States.[157]

Definitive studies on barbiturates and driving have not yet been carried out and the data that do exist are incomplete and difficult to interpret. Road research has been hampered by numerous difficulties including practical problems in determining drug levels in the body at the time of accidents, and the possible confounding effects of other drugs. The role of alcohol in traffic accidents, for example, became more apparent after studies showed that drivers in accidents had higher blood alcohol levels than non-crash drivers who had been using the roads under similar circumstances.[11]

Laboratory studies of psychomotor performance and other psychological functions presumed to be important in automobile driving indicate that barbiturates may produce a dose-related impairment, and that some effects may last up to a day after a large sleep-inducing dose.[91, 92, 104, 109] Under some conditions, low doses of barbiturates may improve performance.[100, 155] As noted earlier, the behavioural effects of barbiturates are very similar to those of alcohol. With high doses of either drug, the user may demonstrate a diminished ability to react quickly and to perform skilled precise tasks (particularly those requiring selective attention). Aggressiveness and risk-taking may increase. Low therapeutic doses may not cause driving problems, but further research is needed. It has been suggested that persons who are very tense may become safer drivers after low doses of barbiturates.[100] Overall, it appears that in high doses barbiturates have the potential for contributing to automobile accidents and that barbiturates in combination with alcohol would be an added hazard.

Psychiatric Complications

Although heavy users of barbiturates may be hospitalized for the treatment of dependence, there is little indication of major psychiatric disorders directly attributable to the effects of these drugs. Acute toxic psychoses are uncommon, although delirium, paranoid symptoms and aggressiveness may be present during heavy intoxication. Short-term psychoses often occur during withdrawal in heavy dependent users. Secondary barbiturate involvement in, or complication of, various psychological problems has been reported in many dependent users. In one study multiple drug users noted more adverse psychological effects with barbiturates than with heroin.[28]

The heavy use of barbiturates and other sedatives may contribute to what has been described as an "amotivational syndrome", characterized by apathy and reduced drive and ambition. It has been noted that the work output of certain barbiturate dependents is minimal, and may generally be lower than that of persons dependent on heroin, for example.[28, 93] Considerable concern has been expressed over the possible adverse effects of

chronic sedative use on the maturation process in adolescents.[156,157] A recent United States Senate committee report on barbiturate use in juveniles summarized the testimony of Sidney Cohen as follows:

> Those involved in the "downer" scene, even if they avoid the associated illnesses, injuries and fatalities, will sustain a significant defect in their personality development. They will have spent long periods during their maturation evading with chemicals the very elements of existence which promote human growth: the frustrations, problems and stress of daily life. It is this aspect of bedrugged adolescence which is particularly tragic—the loss of opportunity to grow up psychologically.[P.4][157]

In the Commission's 1971 national survey of psychiatric hospitals barbiturates were mentioned in the primary diagnoses of 19 (0.08%) and in the secondary diagnoses of 9 (0.04%) of the 22,885 patients in the hospitals at that time.[67,[d]] In British Columbia, general hospitals with psychiatric wards were surveyed as well; barbiturates were noted in the diagnosis of 6 of the 293 psychiatric patients in the reporting hospitals. The national mental health data collected by Statistics Canada for 1971, indicated that barbiturate dependence accounted for 66 (0.11%) of the first admissions and 60 (0.11%) of the readmissions to psychiatric hospitals and wards.[16, 129,[e]] More than half of these admissions involved females and the majority were over 25 years of age. These two sources of data suggest that in 1971 barbiturates were not a significant factor in psychiatric admissions in Canada. (See also Tables A.5, A.6 and A.7 in the Annex to this appendix.)

Crime

At present, barbiturate use does not appear to be a significant contributor to, or correlate of, crime in Canada. In the United States there are indications that barbiturate use is growing, particularly among youth, and an increase in barbiturate-related crime in that country has been noted.[156, 157]

There are several ways in which barbiturate use might be associated with crime. As with alcohol, barbiturates may increase the likelihood of certain individuals becoming aggressive or violent. Persons dependent on barbiturates may commit crimes in an effort to obtain the drug, either by stealing it or by stealing money or property with cash value for the purpose of purchasing the drug. However, because of the ready availability of barbiturates from many legal sources and, consequently, the low price of illicit barbiturates (compared to heroin, for example) this type of barbiturate-related crime is relatively infrequent in Canada. Heavy barbiturate use by some delinquent groups in the United States has been noted,[142] but the role of the drug in their illegal behaviour is not easily interpreted. Barbiturates may be used to gain confidence or to reduce nervousness in preparation for previously planned crimes. Most barbiturate users in Canada (including the majority of dependent users) are apparently adults who live an otherwise socially acceptable existence without significant involvement in criminal activities.

Physiological Effects

The primary short-term physiological effect of barbiturates is a general depression of central nervous system and muscular activity, although the response to low doses may be quite variable. Initially, the electroencephalogram (EEG) may suggest some activation or arousal, but with sufficient dose (e.g., 100–200 mg), this brain wave pattern is usually replaced by signs of drowsiness or sleep.[78, 165] The somnolence induced by barbiturates generally resembles normal sleep with the exception of an initially marked reduction in dreaming and in the rapid eye movement (REM) sleep stage.[45, 120] (REM sleep is thought to be related to dreaming, but its overall significance is only beginning to be appreciated.) With repeated use some tolerance develops to REM suppression. As with alcohol, barbiturates are thought to produce their principal effects by inhibiting activity in the brain stem reticular formation, which among other things, controls sleep and wakefulness. Direct effects on other areas of the brain are likely involved as well.[2]

Drowsiness or 'hangover' symptoms may follow acute barbiturate intoxication or drug-induced sleep. Such 'hangovers' generally lack the nausea and other gastrointestinal disruption associated with alcohol since barbiturates have little irritant effect on the stomach and intestines.

A variety of transient or temporary physiological changes occur with moderate doses; the majority of these reflect a general slowing down of physiological activity which normally occurs with behavioural sedation, and are of little clinical significance. A minor decrease in gastrointestinal and autonomic nervous system activity may occur. The brain centres responsible for the control of breathing are especially sensitive to higher doses, and fatal depression of these mechanisms is the primary danger in barbiturate overdose.[106, 134]

A toxic or poisoned state may be produced by five to ten times the normal sleep-inducing dose, and is characterizd by coma and a general shock syndrome (e.g., weak rapid pulse, shallow breathing, low blood pressure and cold sweaty skin). Larger quantities may be fatal as a result of respiratory arrest, cardiovascular collapse and/or kidney failure. Quantities of 15 to 20 times the usual hypnotic dose may produce death in a matter of minutes; however, if proper treatment is administered before breathing has stopped the chances of recovery are generally good. If the overdose is not fatal, a temporary jaundice (due to impaired liver function), respiratory complications, kidney dysfunction and skin reactions may result. Other damage may occur indirectly as a result of respiratory depression. Some of these toxic reactions may also appear with normal doses in individuals allergic or abnormally sensitive to the barbiturates.[106, 134] Because of the well-documented additive or potentiating effects among many sedatives, users of related drugs, such as alcohol, must be especially attentive to barbiturate dose levels.

Following chronic use of barbiturates there is generally fairly complete recovery from direct drug effects. Other than possible secondary complications of injections in some users, instances of severe physiological disorder, or of irreversible brain, liver, kidney, heart, gastrointestinal or other tissue damage are rarely noted. Barbiturates do not greatly affect eating habits and diet, and consequently nutrition is usually adequate, in contrast to the typical situation of heavy chronic alcohol consumption. Unlike barbiturates, alcohol provides calories and disrupts normal gastrointestinal function.

Chronic barbiturate intoxication may lead to an increased incidence of accidental injuries, including, among others, possible head injury and brain damage. In addition, neglect of personal hygiene and other factors important to health may render some heavy users more susceptible to certain forms of disease and infection. Heavy barbiturate users may also run a greater risk of becoming dependent on alcohol, a condition associated with a variety of health problems, as discussed earlier.

Since barbiturates are highly effective orally and are typically taken by this route even by chronic heavy users, complications caused by injections are less commonly seen than with dependence on heroin or methamphetamine. The popular sodium salts of barbiturates are strongly alkaline and can cause considerable pain and tissue damage if injected under the skin. Abcesses and infections have been reported to result from unsuccessful attempts at intravenous injection. Cases have been reported where barbiturates were mistakenly injected into an artery instead of a vein.[57, 66] Rather than following the normal venous route through the general vascular system in the body, such arterial injections result in immediate high drug concentrations in the small peripheral blood vessels in the extremities. This produces excruciating pain, tissue damage and, in some instances, gangrene which may necessitate the amputation of parts of the hands or feet.

In addition to these possible direct effects of barbiturate injection, further complications including hepatitis, tetanus, malaria, abcesses and ulcers of the skin, and a variety of other infections may be caused by shared or unsterile needles or drugs. Repeated intravenous injections result in scarred veins ('track marks') and other vascular damage. Furthermore, the injection of insoluble or colloidal particles (which are typically present in drug preparations intended for oral use) often damages lung tissue and can be fatal.[4, 135]

Self-Poisoning, Suicide and Accidental Death

The role of barbiturates in poisoning and death is quite different from that of most of the drugs discussed in this report. For decades barbiturates have been cited as a major source of poisoning and the leading cause of drug overdose deaths in North America. In Canada more acute overdose fatalities are attributed to barbiturates than to all other psychotropic drugs combined.[18] Similarly in California, for example, barbiturates were involved

in more than half of all drug-related deaths in 1970–71.[156] The vast majority of the barbiturate-related fatalities in Canada involve deliberate self-poisoning by adults, with or without lethal intent.

In 1971, there were 2,134 non-fatal and fatal barbiturate poisonings reported to the Federal Poison Control Program.[118] Among all pharmaceutical preparations, only acetylsalicylic acid compounds (e.g., Aspirin®) and certain minor tranquilizers (e.g., Valium®) were responsible for more toxic reactions than barbiturates. Relatively few poisonings with these non-barbiturates were fatal, however. Barbiturate cases made up approximately 4% of the total of almost 53,000 poisonings reported for all substances (including drugs, household chemicals, weed killers, insecticides, etc.), but barbiturates were involved in one-quarter of the fatal poisonings reported to the Program. Of those substances noted in the report to "frequently lead to drug abuse" (excluding alcohol), barbiturates accounted for less than one-seventh of the toxic reaction cases, but more than half of the reported fatalities.

The rate of reported barbiturate poisonings in the population was highest for children under five years of age, but overdose fatalities in this group are rare. Adults over the age of 25 had the second highest per capita poisoning rate and accounted for the majority of both non-fatal and fatal poisonings. The proportion of total barbiturate poisonings which was accounted for by persons over 25 has risen slightly during 1965–71. Almost two-thirds of the cases were females. In 1971, of 1,478 instances of barbiturate poisoning where the disposition of the case was specified, 755 (51%) resulted in hospitalization; these patients received a median of four to five days hospital care. There were reports of 89 barbiturate-related deaths, of which 63% included mention of other drugs as well, with alcohol noted in the majority of these latter cases. Only six of the fatal poisonings involved persons between 10 and 24 years of age. Drug interactions in the non-fatal poisonings are not reported, and all cases appear under only one drug category in the official *Poison Control Program Statistics.*

The proprietary barbiturate preparations most frequently mentioned in the 1971 poisoning reports were: Tuinal® (secobarbital and amobarbital, 458 cases); Seconal® (secobarbital, 425 cases); Carbital® (pentobarbital and carbromal, 148 cases); Fiorinal® (butalbital, caffeine, phenacetin and A.S.A., 102 cases); Amytal® (amobarbital, 95 cases); and Nembutal® (pentobarbital, 69 cases). Of 58 fatal reactions where the specific barbiturates were noted, secobarbital or amobarbital, either alone or together as Tuinal®, appeared in 49 (85%) of the reports.

According to the *Causes of death* statistics published by the Federal Government, in 1971 there were 482 drug overdose deaths in Canada which were attributed at least in part to the effects of barbiturates.[15] In 309 cases (64%), barbiturates were the only drugs mentioned, but in 173 cases other drugs were indicated as well, with alcohol noted in 144 instances. These figures undoubtedly underestimate the total involvement of barbiturates

in fatal poisonings. In most areas of Canada, autopsies are not carried out in a large proportion of self-poisoning or suicide cases, and screening for barbiturates in the body is even less common.[113, 152] Furthermore, some barbiturate-interaction deaths involving a variety of drugs are put in a general unspecified category in government statistics and, consequently, cannot be easily identified.[121, [m]]

In 1971 barbiturates were involved in 8.5% of 2,559 deaths attributed to suicide or intentional self-inflicted injury in the official statistics.[15] Of 591 fatal self-poisoning cases involving a group of compounds designated as "solid or liquid substances" (which includes licit and illicit drugs, household chemicals, insecticides, etc.), 217 (37%) of the deaths were attributed to barbiturates, the most frequent toxic agents noted. Of all barbiturate fatalities, there were 283 cases where the circumstances of death had been specified; 77% of these were classified as suicide. This is likely an underestimate of the actual proportion of the total deaths which involved intentional self-poisoning (but not necessarily including fatal intent). In many instances adequate information is not readily available to ascertain the intentions of the deceased and such ambiguous cases are typically left unspecified or are classified as accidents. In addition, there is often considerable reluctance on the part of physicians to designate fatalities as suicides on death reports. Follow-up research indicates that a large proportion of fatal poisonings originally classified as accidents actually involved intentional self-injury or suicide.[29, 152]

Women constituted 78% of the cases reported as suicides and 59% of those designated as accidents in the official 1971 statistics.[15] Quite consistently during 1965–71, approximately two-thirds of the barbiturate deaths have involved persons over 40 years of age. After rising somewhat in the late sixties, the number of barbiturate deaths in Canada has levelled off and declined slightly in the early seventies—reflecting, in part, the shift in medical prescribing away from barbiturates to the minor tranquilizers and non-barbiturate sedatives.

It would appear that relatively few barbiturate deaths in Canada were purely accidental in the sense that they did not involve suicide attempts or intentional self-injury. Fatalities due to overdose in young persons taking barbiturates for the 'trip' or euphoriant effects are quite infrequent and make up a very small proportion of the total number of barbiturate-related deaths.[113] As well, few deaths result from intended therapeutic use of these drugs. Consequently a more detailed examination of the concept and conditions of suicide is appropriate in this discussion.

Many researchers have concluded that the majority of "suicide attempts" might better be called "suicide gestures", and do not actually involve a serious intention of death.[72, 87, 108, 117, 146] Most such acts are considered to be primarily sympathy- or attention-getting devices and are often a plea for help or an attempt to force the subsquent resolution of some personal conflict. Although cases of intentional self-poisoning and suicide frequently

involve 'repeaters' with previous intentional self-injuries, the act is usually impulsive and not carefully planned in advance.[72, 81, 88, 89, 137, 152] Instances where individuals had actually acquired drugs for the purpose of self-injury are apparently infrequent.[24, 81, 82, 107, 137] Typically, the drugs employed had been in the person's possession for some time prior to the poisoning, and were originally acquired through legitimate prescription for medical use. Many self-injuring individuals have a prior history of psychiatric disorder.

The use of alcohol in combination with barbiturates is common in self-poisonings, and a disproportionately large number of persons engaging in suicidal behaviour are problem drinkers. (The significant role of alcoholism in suicide is discussed in more detail in Appendix A.6.) It is thought that a significant number of self-poisoning suicide gestures result in unintended fatalities due to the accidental administration of a lethal dose, especially when the individual has been drinking heavily.[145, 162, 163] Because of these frequently reported patterns, the careless or excessive prescribing of barbiturates for depressed patients, heavy drinkers or persons with a history of self-injury has been severely criticized.[31, 81, 100, 134, 137]

A phenomenon called "drug automatism" is somtimes mentioned in association with toxic barbiturate overdose, although many observers have expressed doubts as to its significance. In this situation, individuals in a drug-induced state of confusion or stupor are said to administer additional quantities of the drug without being fully aware of the extent of previous doses.[106, 134] In Canada, few, if any, such deaths have been documented.

As noted earlier, in the past few years the minor tranquilizers have become more frequently prescribed than the barbiturates.[18, 27] There has been a concomitant increase in self-poisoning with the minor tranquilizers as a result. However, since some of these latter compounds (particularly the benzodiazepines) have very low lethal toxic potential there has been a decline in the proportion of fatal outcomes in the total number of poisoning cases involving sedatives and tranquilizers. Apparently, a reduction in the availability of barbiturates does not necessarily reduce the total number of self-poisonings or suicide attempts, but it may result in fewer overdose fatalities if available alternative drugs are less toxic. The relative toxicity of these various sedatives and tranquilizers, the incidence of related poisonings, and the associated prescribing trends are discussed in more detail below in A.8. *Minor Tranquilizers and Non-Barbiturate Sedative-Hypnotics.*

Tolerance and Dependence

Tolerance to some of the effects of barbiturates readily develops; the degree and rate of its development vary considerably with the particular drug, the dose, the mode and frequency of administration and the individual involved. A phenomenon called acute tolerance (lasting several hours) may occur after a single dose, thus reducing the response to further doses given at short intervals. Depending on the barbiturate taken and the pattern of

use, more prolonged tolerance may begin to appear within days or weeks of daily administration.[7, 70, 77, 94] The extent of maximum tolerance to sedative-hypnotics is quite limited compared to that which can result with opiate narcotics.[85] Barbiturate tolerance occurs to the greatest extent to the mood, sedative and behavioural effects. Tolerance to the lethal toxicity (i.e., respiratory depression) develops more slowly and to a lesser degree. As with alcohol, when general barbiturate tolerance develops the safety margin between the psychologically effective and the lethal dose is narrowed.

Several mechanisms seem to operate in producing barbiturate tolerance.[23, 70, 85] As noted above, barbiturates stimulate the production of metabolic enzymes in the liver which inactivate these and many other drugs. The resulting increase in the rate of metabolism and excretion is primarily responsible for general tolerance. As well, some overall reduction occurs in the sensitivity of the tissues to the drug. Certain learning processes are also likely to be involved in changing the character of the response with repeated use. Tolerance develops more quickly to the shorter-acting barbiturates than to the long-acting varieties, perhaps because of the greater importance of liver metabolism in the inactivation and excretion of the former compounds. Most aspects of tolerance disappear after a few weeks of abstinence from the drug. Some persons may become more sensitive to barbiturates after withdrawal than they were prior to chronic use.[42, 70]

The capacity of barbiturates to produce physical dependence was not generally recognized for decades after their wide medical acceptance, although considerable attention had been directed to problems associated with psychological dependence. A series of experiments by Isbell and associates, published in the early 1950s, clearly demonstrated that chronic use of large doses of barbiturates (i.e., several hundred milligrams per day) can produce profound physical dependence similar to that of alcohol.[51, 74, 75, 76] The abstinence syndrome following withdrawal from large doses of barbiturates may begin with a reduction in intoxication and an apparent improvement in condition. Within a few hours, however, general physical weakness, dizziness, anxiety, tremors (the 'shakes'), hyperactivity, sleeplessness, nausea, abdominal cramps and vomiting may occur. These may be followed after several days by muscle spasms and grand-mal (epileptic) seizures. Between the third and seventh day, delirium, delusions and hallucinations may appear; these and other symptoms may last for days or even months, although general recovery usually occurs within a week or two. As with alcohol, death during the convulsive phase occasionally occurs.[32, 60, 79] In extreme cases the barbiturate- or alcohol-type withdrawal syndrome is considerably more painful and dangerous than that associated with dependence on the opiate narcotics. Withdrawal effects following dependence on more moderate barbiturate doses are considerably less severe than the full syndrome described above. Most regular users of therapeutic doses do not develop significant tolerance or dependence. Babies born of mothers who are physically dependent on barbi-

turates are also typically physically dependent, and may suffer severe withdrawal symptoms if the condition is not recognized and treated soon after birth.[9, 33]

Anxious or tense individuals may become psychologically dependent on even small doses in order to function in a manner which they consider satisfactory; many persons become dependent on barbiturate sleeping pills and feel that they cannot sleep without the drug; others become dependent on a variety of subjective effects which they feel are satisfying or perhaps essential to their well-being.

Barbiturates and Other Drugs

The effects produced by combinations of barbiturates and other drugs may often resemble the interactions described earlier for alcohol. Because of the similarities among the barbiturates and other general sedatives, these drugs are often used interchangeably.[35] Barbiturates combined with alcohol, minor tranquilizers, non-barbiturate sedatives or volatile solvents often result in a more intense and longer-lasting effect than is produced by either drug alone.[23, 49, 80, 98, 99, 168] In addition to direct additive effects, the presence of alcohol in the body may slow the metabolism of barbiturates.[115]

A certain amount of cross-tolerance exists among these drugs and chronic users of barbiturates are generally quite resistant to many of the effects of the other sedatives.[54, 84] This cross-tolerance, however, may not appreciably affect the lethal dose, and large quantities of alcohol and barbiturates taken simultaneously (acting in an additive or potentiating fashion) may produce a toxic or fatal reaction in persons tolerant to other effects. In addition, these drugs generally show some degree of cross-dependence and have the capacity to block or diminish the withdrawal symptoms associated with physical dependence on the other sedatives.[32, 54] Barbiturates are frequently used therapeutically to reduce the severity of withdrawal in alcoholics. Since most sedatives show this cross-dependence, individuals dependent on one may turn to other sedatives if the preferred drug is unobtainable. Consequently, chronic barbiturate dependents are usually heavy alcohol users as well. Most sedatives can also reduce some of the acute 'hangover' symptoms associated with other drugs of this class. Multiple drug users often refer to the barbiturate intoxication as a 'dry drunk'. See A.6 *Alcohol* for further discussion of barbiturate-alcohol interaction.

Little research has been done regarding the interaction of barbiturates and opiate narcotics in humans. It is clear, however, that the dose of either of these drugs which produces sedation, toxicity and death is lower when they are used together. Although barbiturates and opiate narcotics do not show significant cross-tolerance or cross-dependence, barbiturates are sometimes used to reduce the unpleasantness of opiate narcotic withdrawal. Some subjective effects of the drugs apparently interact in a complementary way when used together and barbiturates reportedly modify and prolong the

effects of heroin. Barbiturates are often employed by opiate narcotic users to strengthen or reinforce a weak heroin dose or as a substitute when opiate narcotics are unavailable.[20, 28, 64, 116, 140, 147] Persons on methadone maintenance are frequently reported to use barbiturates and alcohol to get 'high'.[55] The use of barbiturates is not socially acceptable in some opiate narcotic-using groups, however.[28]

Barbiturates are often used in conjunction with amphetamines. The two drugs together may result in some enhanced psychological response, although certain of their central nervous system effects are antagonistic. Amphetamines are sometimes used in the treatment of barbiturate overdose, although the value of such applications is questionable.[37] Likewise, barbiturates are sometimes employed to reduce the toxic effects of stimulant overdose. Dexamyl® is a popular prescription combination of dextroamphetamine and amobarbital which supposedly produces stimulation without the irritability or tension produced by amphetamines. An alternating cycle of sedation and stimulation has been frequently noted among certain medical and non-medical drug users. A stimulant may be used to overcome the drowsy hangover the day after a hypnotic dose of barbiturate. By evening, another sedative dose may be necessary to overcome the insomnia potentiated by the day's amphetamine. A somewhat related pattern has been demonstrated by some amphetamine-injecting 'speed freaks' who use barbiturates to terminate the stimulant effect, 'mellow the crash', or produce sleep after a 'speed run' of several days duration.

Apparently barbiturates are not often used in combination with cannabis, LSD or other hallucinogenic drugs in Canada. In rodent studies cannabis has been found to prolong barbiturate sedative-hypnotic effects, probably in part through metabolic interaction.[56, 58, 96, 124, 154] Commission research showing marijuana enhancement of certain alcohol effects suggests that some interaction might be expected with cannabis and barbiturates.[112, 127] Some concern has been expressed that even though cannabis is not very toxic physically, high doses taken in combination with barbiturates or other sedatives might enhance the toxicity of the latter drugs.[122] In one animal study cannabis was shown to increase sensitivity to barbiturate overdose.[47]

The Commission study of illicit drug samples indicated that LSD-barbiturate mixtures do occur, although they are uncommon.[114] Such combinations would be expected to reduce some of the psychedelic and stimulant effects of LSD.[69] Barbiturates are often used to treat or terminate an LSD 'bad trip'. On some occasions barbiturates have reportedly been mixed with STP or MDA to reduce the amphetamine-like toxic side effects seen with large doses of these latter drugs.[139] It seems likely that barbiturates would enhance the sedative effects of PCP at doses typically taken, but such combined use has not been documented.

Although a number of drugs can block or reduce certain barbiturate effects, there are no known general barbiturate antagonists. The development of radio-immunoassay techniques for the chemical analysis of barbitu-

rates,[101, 143] raises the possibility of a general immunization against barbiturate effects. However, no research in this latter area has been reported. Patterns of multiple-drug use are discussed in more detail in Appendix C *Extent and Patterns of Drug Use.*

A.8 MINOR TRANQUILIZERS AND NON-BARBITURATE SEDATIVE-HYPNOTICS

INTRODUCTION

There are many common drugs which have significant sedative-hypnotic properties. Alcohol and barbiturates have been discussed separately in this appendix, and their many pharmacological similarities were indicated. Barbiturates are often considered the prototype of sedative-hypnotic drugs; pharmacologically related compounds are frequently identified or discussed in terms of their similarities to and differences from them. We shall consider a rather heterogeneous aggregate of sedative compounds in this section under the general rubric of *minor tranquilizers and non-barbiturate sedative-hypnotics.* Because of significant similarities in effects, many of these drugs, and alcohol and barbiturates as well, are often considered together in broad categories given such titles as sedative-hypnotics, psychosedatives, anxiolytic sedatives (or just sedatives), non-selective depressants (or just depressants), ataractics, or psycholeptics.[3, 32, 79, 125]

TABLE A.4

MINOR TRANQUILIZERS AND NON-BARBITURATE SEDATIVE-HYPNOTICS

(1) *Acetaldehyde derivatives*
(e.g., chloral hydrate [Noctec®], paraldehyde)

(2) *Propranediol derivatives*
(e.g., meprobamate [Equanil®, Miltown®], tybamate [Solacen®])

(3) *Benzodiazepine derivatives*
(e.g., chlordiazepoxide [Librium®], diazepam [Valium®, Vivol®], oxazepam [Serax®], nitrazepam [Mogadon®])

(4) *Piperidinedione derivatives*
(e.g., glutethimide [Doriden®], methyprylon [Noludar®])

(5) *Pentynol derivatives*
(e.g., ethchlorvynol [Placidyl®], ethinamate [Valmid®])

(6) *Quinazolone derivatives*
(e.g., methaqualone [Mandrax®, Mequelon®, Quaalude®, Sopor®, Parest®])

(7) *Miscellaneous*:
(a) Monoureides (e.g., carbromal)
(b) Bromides (e.g., Nytol®)
(c) Anticholinergics (e.g., scopolamine, benactyzine)
(d) Antihistamines (e.g., dimenhydrinate [Gravol®, Dramamine®], diphenhydramine [Benadryl®], doxylamine [Decapryn®], hydroxyzine [Atarax®], methapyrilene [M-P®], phenyltoloxamine [Bristamin®], promethazine [Histantil®], pyrilamine [Neo-Antergan®], triprolidine [Actifed®])

A.8 *Minor Tranquilizers and Non-Barbiturate Sedative-Hypnotics*

The minor tranquilizers and non-barbiturate sedative-hypnotics can be divided into several groups as indicated in Table A.4.[3, 79] With few exceptions, the drugs in the first six groups share significant common pharmacological properties and are similar to alcohol and barbiturates in many important respects: these drugs reduce anxiety and tension, and produce drowsiness and sleep at progressively higher doses; they elicit similar psychological and physiological signs of intoxication and overdose; they have relatively little effect on autonomic nervous system functions; they generally elevate the convulsion threshold; limited but significant tolerance develops with chronic heavy use; physical dependence can also occur with high-dose use; psychological dependence is sometimes reported; and significant but often incomplete cross-tolerance and cross-dependence may occur among them.[3, 36, 38, 79, 125] The various drugs may differ to some extent in their potential for producing these effects. The major exceptions to some of these generalizations about sedative drugs are certain anticholinergic (acetylcholine blocking), antihistaminic (histamine blocking) and bromide compounds, although even these are similar to the other sedatives in many respects. In addition, most of the volatile solvents and gases have somewhat comparable sedative properties. Under certain conditions, cannabis has significant sedative or tranquilizing effects and has been used medically in Canada and many other countries for these purposes.[e] Some further distinctions among the various sedative drugs are made in the following discussion.

The term "*minor* tranquilizer" was introduced in the scientific literature in the 1950s to distinguish some of the newer non-barbiturate drugs prescribed to reduce anxiety and tension from the "*major* tranquilizers" or *neuroleptics,* such as the phenothiazines (e.g., chlorpromazine) and rauwolfia alkaloids (e.g., reserpine), which are employed more as antipsychotic drugs in the treatment of such disorders as schizophrenia.[8, 79, 103] The minor tranquilizers are intended to reduce anxiety, tension and agitation at doses which have relatively few other significant effects on emotional, cognitive or perceptual processes. The degree to which they approximate this goal and the extent to which they actually differ in this regard from the various barbiturate and non-barbiturate sedatives is still a matter of some controversy. In this report, and in much of the scientific literature, the label "minor tranquilizer" is restricted to the benzodiazepine and propranediol derivatives (e.g., Valium®, Librium®, Equanil®, Miltown®), but the term is often used in a broader sense to refer to other of the newer non-barbiturate sedatives as well. Although the benzodiazepines are perhaps most unique, few clear pharmacological distinctions can be drawn between most of these sedatives.

Much confusion is caused by the non-specific usage of the general label "tranquilizer". Both major and minor tranquilizers are often indiscriminately grouped together under the broad heading of "tranquilizer" in spite of the fact that these two classes of drugs are quite dissimilar chemically and pharmacologically, and have generally different medical applications and patterns of non-medical use.[8, 32, 33, 79, 107, 122, 125] The major tranquilizers do

not produce euphoria or other pleasant psychological side effects and are consequently rarely used non-medically. The minor tranquilizers, on the other hand, typically produce effects subjectively similar to those of alcohol and barbiturates, and may be used non-medically because of these properties. Dependence on the minor tranquilizers has often been reported in the literature. In spite of significant differences (especially as regards non-medical use), many official and lay sources continue to use the general category "tranquilizer", with no further differentiation, thereby confusing and confounding many important issues.[17, 18]

The sedative effect of bromide was first used in medicine in the 1850s in the treatment of epilepsy. Bromides were soon employed on a large scale for a variety of psychological and neurological disorders. Unlike most other drugs which depress the functioning of the central nervous system, the bromides do not effectively induce sleep in large single doses. They are usually administered chronically for their general cumulative sedative effects. Although bromides are still employed in a variety of nerve tonics, headache remedies (e.g., Bromoseltzer®) and non-prescription 'sleeping pills' (e.g., Nytol®), they have generally been replaced in medical use by a variety of more effective and less toxic drugs.[79, 109]

Chloral hydrate and paraldehyde are very effective sedative-hypnotics which were introduced into medicine in the latter part of the 19th century and are still employed in clinical therapeutics today. Chloral hydrate was the first widely used synthetic sleep-inducing (hypnotic) drug, and as 'knockout drops' added to alcohol produces the so-called 'Mickey Finn'. Both chloral hydrate and paraldehyde have been used in the treatment of alcohol withdrawal. Dependence on these drugs has become rare but is still sometimes seen.[85, 90, 109]

Barbiturates were first used medically in 1903 and dominated the area of sedative-hypnotic therapeutics for the following half-century.[79, 109] Most of the drugs in groups 2 to 6 of Table A.4 were developed in the 1950s or later, and have tended to replace barbiturates in many areas of medical and non-medical use. Many of these sedatives were introduced specifically as "non-barbiturates", suggesting major distinctions in dependence liability, toxicity and certain other effects. In some instances significant differences between barbiturates and the newer sedatives and minor tranquilizers are clearly documented, but many of these drugs have been shown to be more like barbiturates than was originally realized. Compared to the barbiturates, much less is known about the effects of both the medical and non-medical use of these newer drugs. It is interesting to note that thalidomide was introduced into medicine as a non-barbiturate sedative-hypnotic and is a very effective sleep-inducer.

The minor tranquilizers and non-barbiturate sedatives are among the most widely used drugs in medicine. In 1971, a Canadian Medical Association survey suggested that these drugs accounted for half of all mood-modifying drug prescriptions in Canada. In comparison, barbiturates made

up one-fifth of such prescriptions.[19] Valium® (a benzodiazepine minor tranquilizer) is the widest selling prescription drug in Canada.[59]

Until recently, the non-medical use of these sedatives was considered largely the domain of the 'average middle-class adult', but recent reports indicate that some of these compounds are gaining in popularity among youth as well.[51] The non-medical use of Mandrax® (methaqualone and diphenhydramine) and other methaqualone preparations has frequently been noted in Canada in recent months. (See also Appendix C *Extent and Patterns of Drug Use.*)

Atropine and scopolamine (*l*-hyoscine) are belladonna alkaloids which block certain effects of acetycholine in the body. Atropine generally produces central nervous system excitation, but scopolamine has mild sedative properties in moderate doses. In higher doses, however, both belladonna alkaloids have similar effects and may produce delirium and hallucinogenic responses.[27, 50, 58, 62] Scopolamine is found chiefly in *Hyoscyamus niger* (henbane), *Datura stramonium* (Jimson or Jamestown weed, also known as thorn-apple or stink weed) and other *Datura* varieties. These drugs have been used in many societies since ancient times for a variety of medical and non-medical purposes. They were frequent ingredients in sorcerers' potions and poisons, and have served important religious functions in certain cultures.[22, 62, 83] In the United States, scopolamine was commonly employed in non-prescription sedative and motion-sickness preparations, but in recent years it has been removed from many such over-the-counter products. It has not been commonly used for such purposes in Canada. Because of unpleasant side effects at high doses, these drugs are not frequently used non-medically, although a few reports exist, for example, of young people using such stramonium preparations as Asmador® cigarettes for hallucinogenic purposes.

There is a wide variety of drugs which are used medically for their antihistaminic and anticholinergic properties; many have significant central nervous system effects which are of interest here. Since antihistamines were first discovered in France in the 1930s, hundreds of pharmacologically related substances have been identified and synthesized.[12, 34, 106] Many antihistamine-containing preparations are sold in Canada without prescription for use in the symptomatic treatment of a variety of ailments, including the common cold (e.g., Contact®), allergies (e.g., Actifed® [triprolidine and pseudoephedrine]) and motion sickness (e.g., Gravol® [dimenhydrinate]). Labels on many such antihistamine-containing products warn the user that drowsiness may be an expected side effect. The sedative properties of certain antihistamines are made direct use of, alone and with other drugs, in a variety of non-prescription and prescription sedative preparations (e.g., Sominex®, Mandrax®). The antihistamine drugs vary considerably in their sedative properties; some do not exert significant effects on CNS activity or may have mixed stimulant and depressant effects, while a few may rival the barbiturates in their tranquilizing or sleep-inducing capacity.[32, 88, 113] Some antihistamines

produce significant psychological excitation at high doses and hallucinogenic effects have been noted under such conditions.[58, 84] There is apparently relatively little non-medical use of antihistamines alone, although, for example, the use of large doses of Gravol® to get 'high' (often in combination with alcohol) has occasionally been reported among juveniles. Antihistamines with sedative capacity generally have significant anticholinergic properties as well, which may account for some of their central nervous system effects.[109] Consequently, clear distinctions cannot be made between anticholinergic and antihistaminic classifications in many instances.

There are many over-the-counter preparations which are sold as tranquilizers or sedatives. Most contain some combination of bromides, salicylates, anticholinergics, antihistamines or other drugs (e.g., Sominex®, Sleep-eze®, Nytol®, Devarex®, Compoz®). The pharmacological rationale and effectiveness of some of these concoctions has been questioned on numerous occasions, and it would appear that many such preparations are of little or no therapeutic value and may have significant adverse side effects.[76,78,82,83,101]

Medical Use

As with barbiturates, the minor tranquilizers and non-barbiturate sedatives are mainly prescribed for patients suffering from anxiety, tension, behavioural excitement, and insomnia. Some are also used in the treatment of lower back pain, convulsive disorders, withdrawal symptoms of barbiturate-alcohol type dependence, and acute anxiety and panic reactions which sometimes occur with certain hallucinogenic drugs. Some minor tranquilizers are effecitve muscle relaxants.[24, 79, 88, 109]

Some clinicians feel that chemotherapy of anxiety should be a secondary approach in psychiatry (although frequently the most expedient) and that drugs should be used primarily to relieve immediate distress, and to aid the patient only until other treatment procedures become effective.[79]

In addition to their use as sedatives, certain antihistamines (e.g., dimenhydrinate) and anticholinergic drugs (e.g., scopolamine) are employed in the prevention and treatment of nausea and vomiting associated with early pregnancy, motion sickness and other conditions. Antihistamines are commonly used for the symptomatic treatment of hay fever and numerous other allergic reactions. They also relieve nasal congestion and discharge associated with the common cold, lessen rigidity and tremor of parkinsonism, and some are moderately effective local anesthetics.[24, 106] Scopolamine and other belladonna alkaloids are used medically, for example, in the symptomatic treatment of parkinsonism, congestion due to allergies and the common cold, peptic ulcer, and bed-wetting, and are employed in conjunction with other drugs in certain anesthetic applications.[27, 62]

Chemical Analysis of Illicit Samples in Canada

There has been relatively little chemical analysis of illicit minor tranquilizers and non-barbiturate sedatives in Canada. None was mentioned in Marshman and Gibbins' 1970 report from Ontario.[86] The Health Protection Branch special study of police seizures does not focus on these substances, but methaqualone was identified in 20 samples combined with other drugs.[54, b] There were 18 samples involving methaqualone and an antihistamine; LSD was also present in 14 of these cases and heroin was detected in four. There were also two samples of LSD and methaqualone together. These samples contained a median of 20 mg (range: 11–77 mg) of methaqualone per unit dose and approximately 2 mg per capsule of the antihistamine was typically found.

In the Commission's collection of illicit drug samples and our national survey of authorized analytic facilities (1971–72), 15 samples of high purity methaqualone were found along with two LSD-methaqualone combinations.[93, c] Of the unmixed methaqualone samples, two had been represented as mescaline, five as Mandrax® and eight were of unspecified identity. In addition, four samples of chlordiazepoxide, and one each of diazepam, oxazepam, ethchlorvynol and methyprylon were reported. No antihistamines were noted in this study. Two samples of plant materials containing belladonna alkaloids were found.

Administration, Absorption, Distribution and Physiological Fate

The minor tranquilizers and non-barbiturate sedatives are usually administered orally as tablets, capsules or elixirs, but some are occasionally injected for both medical and non-medical purposes. These drugs are generally rapidly absorbed by the stomach, intestine and rectum, and absorption after oral administration is typically most rapid with an empty stomach. Once absorbed, the drugs are generally distributed quite uniformly throughout the body. Some are metabolized, or otherwise chemically altered (usually in the liver), and excreted into the urine, while others are eliminated unchanged. As with barbiturates, some of these drugs increase the body's production of the enzymes responsible for their metabolism. Certain of these substances may be detected in the urine for several weeks after use is discontinued. The factors of distribution, metabolism, and excretion are responsible for many of the differences in potency and duration of action of these drugs.[14, 32, 88, 109, 122]

Methods of detection of some of these drugs and their metabolites in urine and blood are sophisticated and expensive, while others are readily identified with standard analytic techniques.[23, 30, 39, 64, 115, 123] There are currently no immunoassay methods available for any of these sedatives.

General Effects

With most of these drugs, psychological and behavioural responses to low doses are quite variable. There may be sedation in some instances and, in others, an increase in activity. Studies reveal that complex interactions between the specific drug and the level of anxiety may occur, even within the same pharmacological group; psychological and behavioural performance may be impaired or improved, depending on the dose, personality of the user and the degree of anxiety present.[32, 79]

Normal doses usually provide relaxation, a feeling of well-being and perhaps some loss of inhibition—effects not unlike those associated with social alcohol drinking. The response to moderate and high doses of most of these sedatives is a general depression of nervous and muscular activity and certain other body functions. Compared with other sedatives, minor tranquilizers are thought to have less inhibitory effect on the parts of the brain which are responsible for arousal and motor control, and may have greater muscle relaxant effects.[32, 38, 79, 88, 109] The taming effect of minor tranquilizers in animals has frequently been observed.[9, 57, 118] As noted earlier, certain antihistaminic and anticholinergic drugs produce considerable excitation in high doses; hallucinogenic effects have been reported with some of these substances.[50, 58, 78, 84]

Excessive use of most sedatives may produce drowsiness, ataxia, lethargy, disorientation, confusion, memory impairment, trance-like episodes, double vision, personality alterations, rage reactions, and other symptoms resembling those of drunkenness. Other side effects observed with certain of these sedatives include skin rashes, nausea, diminished sex interest, menstrual and ovulatory irregularities, blood abnormalities and increased sensitivity to alcohol.[32, 79, 88, 109]

The national mental health data collected by Statistics Canada for 1971 indicated that dependence on non-barbiturate sedative-hypnotics and minor tranquilizers (ICDA—304.3) accounted for 51 (0.09%) of the first admissions and 33 (0.06%) of the readmissions to psychiatric hospitals and wards. More than half of these admissions involved females and the majority were over 25 years of age. These data suggest that in 1971 these drugs were not a significant factor in psychiatric admissions in Canada.[•] (See also Tables A.5, A.6 and A.7 in the Annex to this appendix.)

Driving

The current knowledge regarding the role of minor tranquilizers and non-barbiturate sedatives in automobile accidents is somewhat similar to that described for barbiturates. Existing data suggest that these drugs have not contributed greatly to highway crashes.[71, 97, 114, 121] In Canada it is an offence to drive while intoxicated by any drugs, and the penalties are the same as those for drunken driving. Traffic convictions involving drugs other than alcohol rarely occur, in part because of the difficulties in proving intoxication.

A number of studies have attempted to estimate the incidence of drug use in the general population, in the driving population, and in the victims of automobile crashes; other reports have focussed on the driving records of individuals known to be users of one or another drug. In general these data have proven to be incomplete and frequently difficult to interpret. There is a clear need for further research in this area. Such research should include emphasis on the chemical detection of drugs in the body fluids or tissues of drivers involved in crashes as compared to persons not involved in such accidents but using the roads under similar circumstances.

Laboratory studies have shown that large quantities of some minor tranquilizers and non-barbiturate sedatives can disrupt performance on certain psychomotor, intellectual and perceptual functions—suggesting that with sufficient dose such drugs may have the potential for increasing the likelihood of automobile crashes. Ordinary clinical doses may not have such effects.[72, 80, 81, 119] Certain antihistamines and belladonna alkaloids might disrupt performance on tasks related to driving, but little relevant research exists.

In one study the accident rate in a group of drivers using prescribed doses of Librium® was ten times the accident rate for the general population, but it is not clear whether the accident rate among these drivers, who "needed" a tranquilizer, was so high because of, or in spite of, the drug they were taking.[37, 79]

Toxicity, Poisoning and Death

As with barbiturates, the majority of serious overdose cases with the minor tranquilizers and non-barbiturate sedatives involve adult intentional self-poisoning (although not necessarily with fatal intent). Much of this literature was reviewed previously in A.7 *Barbiturates*. The number of poisonings or toxic reactions involving these various drugs is generally related to their availability through medical prescription.[92] However, the various sedatives differ considerably in their lethal toxicity,[13, 79, 99, 112, 123] and certain compounds (e.g., the benzodiazepine derivatives) which are involved in many poisonings, may result in very few deaths. It should be noted that official mortality statistics must be interpreted with caution. In many cases autopsies are not performed and a thorough drug identification and chemical investigation of the cause of death is often not conducted.[92, 117]

In the 1971 *Poison Control Program Statistics* there were 4,966 poisonings attributed to "tranquilizers" (both the major and minor categories together) and 1,588 to non-barbiturate sedatives and hypnotics.[96, 97] Diazepam (Valium® or Vivol®) accounted for 2,758 toxic reactions and was second only to acetylsalicylic acid compounds (e.g., Aspirin®) as a source of poisoning in Canada. Chlordiazepoxide (e.g., Librium®) was noted in 922 cases, oxazepam (e.g., Serax®) in 62, a chlordiazepoxide and bromide combination (Librax®) in 60, and meprobamate (e.g., Equanil®) in 52. Females outnumbered males by almost two to one in these data. Approxi-

mately one-quarter of the minor tranquilizer poisonings occurred in children under five years of age, but none of these cases was reported to be fatal. There were 23 drug death reports which mentioned either diazepam or chlordiazepoxide; in 20 of these cases other drugs were specified as well. Three fatal poisoning reports mentioning only Valium® were generally incomplete. One meprobamate interaction death was reported. It should be noted that well-documented cases of simple overdose deaths involving chlordiazepoxide or diazepam are rare or non-existent in the scientific literature.[10, 28, 29, 59, 79, 99]

The Poison Control Program category of "other sedatives and hypnotics" contains a heterogeneous group of chemicals.[96] Methaqualone-containing compounds were reported in 437 cases, with Mandrax® noted in 391 of these. One methaqualone death (Mandrax® and Librium®) was reported. The other most frequently named sedatives were: Noludar® (methyprylon), 264 cases; Placidyl® (ethchlorvynol), 147 cases; Doriden® (glutethimide), 85 cases; and chloral hydrate, 53 cases. There were 12 deaths involving these latter drugs, primarily as interactions with other compounds.

There were also 80 toxic reaction cases involving Sominex® preparations (typically containing bromides, antihistamines and other substances)[16] and 42 Nytol® (bromides) reports. Listed separately were 160 Gravol® and 133 Actifed® toxic reactions. Poisonings with other antihistamines were noted as well. There were no deaths attributed to any of these latter drugs.

Including drug interaction deaths, the number of fatalities reported per thousand poisonings were: 59 for barbiturates, 10.7 for non-barbiturate sedatives (and meprobamate) as a group, and 6.3 for the benzodiazepine minor tranquilizers. If only single drug fatalities are considered, the corresponding rates for these three drug groups are 25.8, 3.3 and 0.8 respectively. In other words, excluding drug interaction reports, barbiturate poisonings were 7.8 and 32 times as likely to be reported fatal as were the non-barbiturate sedative and the benzodiazepine minor tranquilizer cases respectively.[k]

Because of the variety of different compounds subsumed under the topic of minor tranquilizers and non-barbiturate sedative-hypnotics, it is not possible to derive a clear picture of the fatalities involving these drugs from the *Causes of death* statistics published by the Federal Government.[18] These various drugs are often not differentiated or specified in official statistics and are frequently considered together with many other psychotherapeutic agents —particularly when drug interaction is involved.[m]

In the *Causes of death* report for 1971, 32 deaths were ascribed to "tranquilizers" in general.[18] A detailed list of the specific drugs involved revealed that four deaths were attributed to diazepam, one to chlordiazepoxide and four to meprobamate.[98] The remainder involved major tranquilizers. A similar situation existed for 1969 and 1970 as well, when 12 and 15 deaths respectively were ascribed to the former three drugs. Over the three-year period, two-thirds of these individuals were women and approximately two-

thirds of the cases had been designated as suicides. No specific information is available from these government statistics regarding interactions involving these and other drugs.

In the same 1971 report, 61 deaths were attributed to non-barbiturate sedatives and hypnotics alone, with an additional 29 noted in combination with alcohol.[18] Little other specific information is available regarding fatalities due to interactions of these and other drugs. Only three fatalities involving persons under 20 years of age were noted and these were in the 15–19 age category. The majority of the deaths occurred in persons over 40 years of age. Chloral hydrate, paraldehyde, or bromides were specified in four cases, but all other non-barbiturate sedatives were pooled in a single class in the official statistics. There is no methaqualone-specific category in these statistics, but our survey of provincial coroners indicated that a number of drug-related deaths in young people have involved methaqualone—usually in combination with other drugs.[56, 61] We have no reliable information on the extent of such occurrences.

For 1971, there was a total of 99 deaths which involved minor tranquilizers or non-barbiturate sedatives, alone or in combination with other drugs, in the official national statistics.[18] In contrast, there were 482 barbiturate-related deaths for the same period. After adjustment for the number of prescriptions issued (using the Canadian Medical Association's prescription estimates[19]), barbiturates were approximately 100 times as likely to be associated with drug overdose fatalities (per prescription) as were the minor tranquilizers (benzodiazepine and propranediol derivatives) and more than three times as likely as the other non-barbiturate sedatives as a group. In a United States report, the incidence of suicide with barbiturates was 32 times the incidence of suicide with "minor tranquilizers" (meprobamate or chlordiazepoxide), and 2.8 times as great as that involving "new non-barbiturate hypnotics", when related to prescriptions written.[10]

The variation in fatalities among these drugs is possibly due to a combination of factors, including differences in: direct lethal toxicity, interaction with other drugs, drug-induced confusional states, potentiation of emotional depression, unit dosage size, number of doses per prescription and certain personality characteristics and disorders of the persons involved. Further research in this area is clearly indicated.

Tolerance and Dependence

Tolerance can develop to most of the effects of these sedatives with regular use, and the dose may be increased by some users in order to maintain the desired effects. Although originally introduced as 'non-habituating', most of these drugs have been shown to be capable of producing both psychological and physiological dependence resembling that seen with alcohol and the barbiturates. Physical dependence is infrequently seen, but can occur with sustained use of large doses of almost all of the drugs in groups 1 to 6 of

Table A.4. Significant tolerance and dependence generally does not occur with therapeutic doses.[32, 36, 40, 61, 65, 79, 110] Some tolerance to the sedative effects of the anticholinergic and antihistaminic drugs may develop with regular use, but dependence has not been reported.

The clinical descriptions of the abstinence syndrome following abrupt withdrawal after excessive use of some of these drugs indicate a marked similarity to one another and to those of alcohol-barbiturate dependence. The syndrome may be characterized by anxiety, apprehension, tremulousness, muscle twitches, insomnia, headache, rapid pulse rate, fever, loss of appetite, nausea, vomiting, abdominal cramps, sweating, fainting, hyperactive reflexes, convulsions, and uncontrolled urination and defecation. In addition, delirious states can occur with motor agitation, hallucinations, delusions, disorientation and confusion. After very heavy daily use for long periods of time, the abstinence syndrome can be very serious, and a few deaths have been attributed to withdrawal from some of these drugs.[38, 39]

Minor Tranquilizers, Non-Barbiturate Sedatives and Other Drugs

Although these various sedatives have many common features, as noted earlier, there may be significant differences in certain effects, and all of the sedatives cannot be expected to interact with other drugs in the same way. Since the number of different compounds under consideration is large, determining interaction effects for all possible drug combinations would be an enormous undertaking. So far such interactions have generally been investigated only superficially, and consequently only the most general statements are possible. Some of the following topics have been covered in more detail in the previous discussions of alcohol and barbiturates.

Recent detailed studies of alcohol-meprobamate interaction conducted by researchers at the Addiction Research Foundation of Ontario and Rutgers University are indicative of the complexities of this topic. The direction and intensity of the interactions of these two drugs were shown to depend on various dose, time and administration factors, as well as the particular response examined.[20]

Under many conditions, combinations of the various sedative drugs may result in more intense and longer lasting effects than are produced by a given dose of one of the drugs administered singly. Some antihistamine and anticholinergic drugs may also enhance the effects of other sedatives at certain doses.[6, 15, 26, 35, 45, 124]

Cross-tolerance and cross-dependence occur among many sedative drugs.[61, 65] Persons dependent on one of these drugs may turn to the others for a desired effect. Minor tranquilizers and other sedatives are often used to reduce the severity of the alcohol withdrawal syndrome. The development of cross-tolerance among the sedatives does not appear to significantly affect the lethal dose and large but sub-toxic doses of each drug, if taken together, may produce a toxic or fatal reaction in persons tolerant to other effects.

Very little research has been done regarding the interaction of opiate narcotics and the various minor tranquilizers and other sedative drugs. It is expected that certain effects of these drugs would add in such a way that the doses which produce sedation, toxicity and death are lower when they are combined.

The interaction between the various sedatives and the stimulants is complex, with some responses being additive, and others dominated by one or the other drug. Certain sedative effects may be antagonized by stimulants. Various sedatives are reportedly taken in alternation with stimulants by a variety of users. As an extreme example of this phenomenon, intravenous users of amphetamines may take sedatives to ease the discomfort of the 'crash' at the end of a long 'speed run'.

A.9 VOLATILE SUBSTANCES: SOLVENTS AND GASES

Introduction

The inhalation of volatile substances and gases for non-medical purposes has been known for centuries, although it has only been within the last decade that such practices have come very commonly to the attention of public health officials.[11, 17, 34, 36, 46] While recent occurrences of adolescent 'glue sniffing' have received the most publicity, a wide variety of other substances and practices have been involved. These drugs have frequently been labelled *deliriants*, although delirium is only one of many potential effects and is clearly not restricted to these substances. Some of these drugs have much in common with the sedatives (such as alcohol and barbiturates) and might be considered in a sub-class of that group. In addition, certain solvents and gases apparently have some psychedelic or hallucinogenic properties and, in sufficient doses, are anesthetic.

Many of the chemicals used may be described as volatile hydrocarbon solvents and are highly soluble in lipids (fats)—a major component of living tissue. Most of the substances are either gases at room temperature or rapidly evaporate from a liquid phase to a gaseous state when exposed to the air. This property makes them highly desirable, industrially, in the production of materials in which fast drying is essential. The solvents are also usually highly flammable.

There are literally hundreds of easily accessible forms of these materials, which may run from hardware store and cosmetic sundries to clinical drugs and anesthetics. Some common products which may contain large quantities of these chemicals are: fast drying glues and cements; many paints, lacquers and varnishes, and their corresponding thinners and removers; gasoline, kerosene and various other petroleum products; lighter and dry cleaning fluid; fingernail polish remover; and various aerosol products. Active chemicals in these materials include toluene (also called toluol or methylbenzene), benzene, acetone, naphtha, hexane, cyclohexane, trichlorophane, trichloroethylene,

perchlorethylene, carbon tetrachloride, chloroform, ethyl ether, and various alcohols, ketones and acetates. Closely related chemically to the solvents are the freon gases which are commonly used as aerosol and refrigerant gases. Nitrous oxide (often called "laughing gas") and related nitrites are also highly volatile substances with long histories of non-medical use. It was recently observed that 38 different products containing such substances were available from the shelves of a single service station-hardware store in Ottawa.

It is clear that we have in this drug category a large aggregate of chemically diverse substances from a wide variety of sources. While this heterogeneity precludes any broad and all-encompassing generalizations, many of the substances have common properties which warrant general consideration.

Most of these drugs have not been investigated individually in much detail, since only a few have had extended medical use. There has been little systematic pharmacological investigation of the deliberate and repeated inhalation of solvents. In most instances, human studies have been limited to gross investigations of toxicity in industrial situations which have limited application in this context.[24, 29, 32, 58, 67] Some significant information can be gleaned from individual clinical case study reports of intentional users.

Nitrous oxide, ethyl ether and chloroform, three of the best known inhalant anesthetics, had considerable non-medical recreational use which preceeded their general medical acceptance. In 1844, the following advertisement was circulated in Hartford, Connecticut:

> A Grand Exhibition of the effects produced by inhaling Nitrous Oxide, Exhilarating or Laughing Gas! will be given at Union Hall this (Tuesday) Evening, Dec. 10th, 1844.
>
> Forty gallons of Gas will be prepared and administered to all in the audience who desire to inhale it.
>
> Twelve Young Men have volunteered to inhale the Gas, to commence the entertainment.
>
> Eight Strong Men are engaged to occupy the front seats to protect those under the influence of the Gas from injuring themselves or others. This course is adopted that no apprehension of danger may be entertained. Probably no one will attempt to fight.
>
> The effect of the Gas is to make those who inhale it either Laugh, Sing, Dance, Speak or Fight and so forth, according to the leading trait of their character. They seem to retain consciousness enough not to say or do that which they would have occasion to regret.
>
> N.B.—The Gas will be administered only to gentlemen of the first respectability. The object is to make the entertainment in every respect, a genteel affair.[17]

Although this event occurred before the systematic investigation and general medical acceptance of nitrous oxide as an analgesic and anesthetic, the promotors of the entertainment showed considerable appreciation for

the variety of potential effects of the drug and the importance of the individual personalities of those taking it. The non-medical use of nitrous oxide apparently continued on a small scale, and recently seems to be coming back into vogue in North America.

During the century before ether was established in medical practice, it was widely used as an industrial solvent and often as an intoxicant. It frequently served as a replacement beverage for alcohol during times of liquor scarcity in numerous areas in Europe, Great Britain and North America in the 19th century. During World War II, ether consumption increased in Germany when alcohol became unavailable. Inhalation of small amounts of ether and chloroform on special occasions is reported to have been accepted practice in certain sophisticated social circles in North America before the turn of the century.[16]

Ether inhalation parties were not uncommon during the 19th century, especially among students and associates of the healing professions. In fact, it was the observation of one of these ether 'jags' which directly led to the first medical use of ether as a clinical anesthetic by C. W. Long. Soon after, Oliver Wendell Holmes suggested the word *anesthesia* to describe the state of "insensibility" which accompanies the unconsciousness or sleep induced by large doses of these substances.[17]

Although non-medical use of volatile substances has been reported across age groups and spanning social class, recent surveys concur with the law enforcement and public health impressions that use is predominantly a phenomenon of youth, reaching a peak in early teens and dropping off soon after. (See Appendix C *Extent and Patterns of Drug Use.*)

(For federal and provincial provisions with respect to volatile substances see Appendix B.8 *Sources and Distribution of Volatile Substances: Solvents and Gases.*) The almost unlimited number of potential substances makes specific legislation of questionable value as a deterrent. It has often been suggested that manufacturers add to the products most commonly used, a substance which renders the original material offensive to the user. An irritant chemical or obnoxious odour might serve this purpose, although it might also be unpalatable to the manufacturing staff and the legitimate user of these products as well. In Canada, at least one major producer of airplane glue has experimented with mustard oil in this connection.[14] The pervasive use of highly volatile, potentially psychoactive substances for largely non-drug purposes in our society makes this approach seem impractical as a general solution. Furthermore, restricting certain chemicals would have little overall effect since many materials, such as gasoline, are easily obtained by any age group. Effective restriction of access to most such substances could not be achieved except at considerable inconvenience to a large segment of the population. This is an area which clearly calls into question the potential of the crimino-legal system in controlling non-medical drug use.

Medical Use

Most of the volatile substances have had no regular medical use although in many instances the general effects produced are similar to those of the clinical inhalant anesthetics. Ether, nitrous oxide, trichloroetheylene (Trilene®) and chloroform have been widely used as anesthetics, to reduce pain and produce unconsciousness prior to and during surgical and dental work, and at one time they were used as sedatives. Other nitrogenous compounds (e.g., amyl nitrite) are used in the therapy and relief of heart pain and, occasionally, asthma.[17, 46, 50]

Administration, Absorption, Distribution and Physiological Fate

In many instances the active agents in the substances used would be absorbed if taken orally, although inhalation generally provides a more rapid and effective means of administration and a sharpening of effects. Techniques used in inhalation are usually designed to maximize the gas concentration in the air. Frequently the substance is emptied or sprayed into a plastic or paper bag, which is held tightly over the nose and mouth, and the fumes inhaled. Alternatively, a cloth may be dipped in a liquid or the active substance otherwise applied to the cloth, which is then rolled up and held against the nose and/or mouth and the vapours sucked in. In other instances, the drug might be sniffed directly from an open container or inhaled through a tube. Aerosol gases have sometimes been sprayed directly into the mouth. Nitrous oxide is often inhaled directly from tanks (such as those used in medical and dental work, or in soda fountain dispensers), and is sometimes sold in balloons for non-medical use. Amyl nitrite is available in ampules or 'pearls' which are broken to release the fumes.

As noted earlier, the drinking of certain relatively pure substances, such as ether, has also been reported. The effects of oral administration are said to be in many ways similar to those of ordinary alcohol. The somewhat different initial effects of solvent inhalation are probably due to the more rapid rate of absorption from the lung, as compared to the gastrointestinal tract. These observations again underline the importance of route and rate of administration in determining drug effects.

In certain cases some metabolism occurs in body tissue, although many of these drugs are eliminated, chemically unchanged, by the lungs in gaseous form. Consequently, the odour of the substance may be noticeable on the breath for several hours after use. Some solvents are primarily excreted in the urine. Most of the common volatile substances can be chemically detected in either the urine, blood or breath of users.[16, 18, 57]

Effects

The psychological and physiological effects of the volatile solvents are in many respects similar to those produced by alcohol, barbiturates and other

sedatives. Low doses can elicit considerable behavioural and psychological arousal, while higher amounts usually result in sedation and a general reduction in activity. Little is known as to the specific mechanism by which these substances exert their action. As with most drugs, the effects of the volatile solvents and gases can be expected to vary considerably with the individual, his mental set, and the setting in which the substance is used.

Little controlled research has been conducted on the psychological effects of the solvents. Frequently reported are a lessening of inhibitions, a feeling of sociability and well-being, and a general elevation of mood. Higher doses may produce laughing and silliness, feelings of floating and being "out of contact", dizziness, perceptual distortions of time and space, and illusions. Certain of these substances are said to have subjective effects which are in some respects similar to those produced by the psychedelic drugs. In addition, confusion, drunkenness, slurred speech, blurred vision, a feeling of numbness, nasal secretion, watering of the eyes, headache, incoordination and, not infrequently, nausea and vomiting may also occur.[48, 67] As the dose is further increased, the general sedating-anesthetic effects dominate, and drowsiness, stupor, respiratory depression and, finally, unconsciousness result. Extreme quantities may inhibit breathing and produce death.

During the acute phase of intoxication, judgment may be impaired, and considerable confusion, hyperactivity, and lack of behavioural control may occur. Some individuals become irritated, tense, or frightened, and acute psychoses have been noted. There is no evidence of long-term psychotic reactions, however. Reported results of such conditions include accidents, panic, self-destructive behaviour, physical aggression, and other antisocial acts.[19, 68]

The acute effects may be as short as five to ten minutes or last up to an hour, depending on the substance used, the dose administered, and a variety of other factors. Most of these agents are short-acting. Users frequently retain their supply and repeat the administration over several hours, attempting to maintain a balance of intoxication often close to, but below that producing unconsciousness. The state achieved is somewhat analogous to light clinical anesthesia, where mixed stimulation and depression of various psychological and physiological systems occur. Because of the sensitivity of the nervous system to subtle changes in dose, maintaining this level of intoxication is frequently not an easy task, and undesired 'conk-outs' may occur.

Medical anesthetists, in trying to achieve deep anesthesia in a patient with high doses, generally attempt to pass through this early deliriant stage quickly and may use a variety of techniques and other drugs to minimize the erratic stimulating effects of light anesthesia. Many individuals may be able to recall the dream-like experiences and unusual feelings and thoughts which are characteristic of 'going under' with inhalant anesthetics. Such experiences are not unlike the intoxication effects sought by some individuals in the non-medical use of these substances.

The majority of recent reports on volatile solvent inhalation have been concerned with juveniles who had come to the attention of the authorities because of some antisocial or delinquent behaviour, which may or may not have been associated with drug use. Most of these individuals had emotional or behavioural difficulties prior to the use of the drug, and no careful investigation has been done with non-delinquent solvent users, even though there are indications that these latter individuals may make up the majority of users. Little adequate information is available on the long-term psychological outcome of chronic solvent inhalation, although many observers have expressed concern over possible adverse effects of heavy drug use by young people coping with the already trying and often troublesome stage of early adolescence.

In one of the first systematic studies of adolescent glue sniffers, Massengale and associates were unable to find any evidence of significant effects of solvent use on physical health.[43] Although the authors discovered no neurological or intellectual abnormalities, they felt that glue use was a prominent complicating factor in the delinquency of many of their 27 patients. The majority of the solvent users were poorly adjusted to school, had few friends, were generally withdrawn, and were similar psychologically to adult alcoholic patients. Other investigators have also failed to find evidence of irreversible effects on intellectual functioning in chronic glue sniffers.[22]

Temporary changes or abnormalities resulting from acute intoxication with some solvents have been reported in kidney and liver function, bone marrow activity, and a variety of psychological and neurophysiological tests. Gastroenteritis, hepatitis, jaundice, blood abnormalities and peptic ulcers are among the complications reported to be associated with the use of some of these products. In addition, some chronic users have developed slow-healing ulcers around the mouth and nose.[4, 9, 39, 42, 49, 67, 68, 71] The frequent loss of appetite, and resulting poor eating habits, in chronic users may complicate the situation further, and weight loss and various nutritional disorders have also been reported. It appears so far, however, that after discontinuing drug use, complete recovery from these disorders usually occurs. There is little unequivocal evidence of permanent brain damage or other nonreversible psychological or physiological abnormalities due to the deliberate inhalation of these chemicals. Many solvents have not yet been investigated, however, and generalizations about potential dangers from existing data cannot be extended to the vast number of unstudied volatile substances. We have found no evidence that volatile substances are responsible for a significant number of psychiatric admissions in Canada.

While the commonly held belief that permanent brain damage is a regular result of glue sniffing is not supported in the scientific literature, numerous industrial studies involving related chemicals, as well as certain laboratory animal experiments, suggest that irreversible physiological and psychological changes might occur with prolonged exposure to some solvents. As noted earlier, gases (such as freon) are sometimes sprayed directly into the mouth

and throat from aerosol cans. The hazards of such practice include the possible freezing of lung tissue and anoxia.[13]

In the past few years, a number of deaths have been attributed to volatile solvent use.[45, 68] The majority of these fatalities have occurred when the user was inhaling alone, and appear to be due to mechanical suffocation which was subsequent to unconsciousness produced by the drug. Simple unconsciousness, if of short duration, might be quite harmless since fresh air usually produces complete and rapid recovery. However, if the user's mouth and nose is covered by a plastic bag, as is often used for inhalation, suffocation may occur. Also, if the user's face remains close to the vapour source after he loses consciousness, he may continue to breathe fumes which could produce further overdose and respiratory arrest due to depression of the brain-stem breathing centres. A few fatalities have been attributed to vomitus suffocation and, perhaps, damage to lung tissue. In addition, a small number of solvent sniffers in North America have died suddenly and unexpectedly without suffocation, general CNS depression, or gross organic injury.[7] Such infrequent but clearly identified sudden sniffing deaths can result after only a few deep inhalations and have generally occurred under conditions of considerable physical activity or stress. Direct cardiac arrhythmia and arrest may be responsible in some cases.[3, 4, 52, 59, 60]

The Commission has investigated in considerable detail reports of volatile solvent poisoning and death in Canada.[44] The Federal Poison Control Program has records of 174 cases of solvent sniffing poisonings occurring in 1971.[f] Six of these were fatal. The most common materials involved were nail polish remover (84 cases), glue (68 cases) and paint thinner (18 cases). Males outnumbered females by two to one in these data, and most of the cases involved persons between 10–24 years of age. The Commission's study of provincial coroners' reports provided detailed information on ten deaths attributed to deliberate solvent inhalation in Canada during the years 1968–71.[31,s] Eight of the ten cases occurred in Ontario, nine were males and all were between 10 and 18 years of age. In nine of the cases, the deceased was found with a plastic bag over his face. Asphyxia and pulmonary edema were commonly noted. It would appear that the vast majority of solvent deaths in North America would have been avoided if some method of administration not involving plastic bags had been employed.

Tolerance and Dependence

Although no tolerance occurs with occasional use, the chronic user of some volatile substances may require several times as much of the active material to achieve the desired state of intoxication as was originally necessary in the beginning.[28] The possibility of physical dependence with withdrawal symptoms has not been adequately investigated to date, although existing clinical reports suggest that it does not occur. This is somewhat surprising given the pharmacological similarities between the volatile solvents and the

sedatives, which do produce both tolerance and physical dependence. Furthermore, cross-tolerance between the sedatives and solvents has been suggested by the frequently reported insensitivity of chronic alcohol and barbiturate users to ether anesthesia. It is possible that such factors as the rapid excretion of most volatile solvents and/or the usual intermittent patterns of use make the development of physical dependence unlikely, since sustained tissue concentration is very probably an indispensable factor in the establishment of such dependence.

Symptoms of psychological dependence and compulsive use have been recorded, although chronic use is not frequent. Certain regular users reportedly become restless, irritable and depressed if they cannot have access to the drugs.

Solvents and Other Drugs

As noted above, cross-tolerance seems to occur between some solvents and the sedative drugs. It has been noted that solvents are taken in conjunction with alcohol by certain individuals.[5] Alcohol has been shown to augment the adverse effects of trichloroethylene on visual-motor performance.[23] Barbiturates also intensify the effects of certain solvents.[37, 38] Interaction with other CNS depressant drugs would also seem likely, but little research in this area has been conducted. Ether and cannabis did not show significant interaction in a study with mice.[26]

The use of drugs currently available on the illicit market, such as marijuana and amphetamines, has been reported in some youthful solvent users. Adult users of solvents often have a history of heavy alcohol consumption and may switch from one drug to the other. Although some observers entertain the hypothesis that chronic use of solvents in early youth may predispose one to the misuse of other drugs (especially alcohol) in later life, there is, as yet, no empirical evidence to confirm or deny a causal link between solvent use and the use of other drugs. It would appear that solvents are often the substances chosen for non-medical use by very young people primarily because of their ready availability to anyone. Subsequent drug preferences and use patterns may merely reflect an expansion of the options available.

Nevertheless, in view of the generally accepted psychological principle that early significant life experiences tend to be more persistent and to play a more important role in the formation of future behavioural tendencies than later experiences, e.g., during or after adolescence, it would seem reasonable to assume that children who have been repeatedly exposed to the exciting and subjectively rewarding effects of repeated manipulation of mood and consciousness with chemical substances might be at higher-than-average risk to become predisposed to indiscriminate multiple-drug use in later life. (See also Appendix C *Extent and Patterns of Drug Use.*)