MINOR TRANQUILIZERS

76. The term 'minor tranquilizers' was introduced into the scientific literature in the 1950s to distinguish the medicines prescribed to reduce anxiety and tension from the major tranquilizers, like reserpine and chlorpromazine, which are employed (as antipsychotic drugs) in the treatment of severe mental illness such as schizophrenia. Another phrase, often used interchangeably with the words 'minor tranquilizers' is anxiolytic sedatives.
This class of drugs may be defined as substances which reduce anxiety, tension and agitation without other significant effects on cognition or perceptual processes.

It seems safe to say that the optimal anxiolytic sedative, which effectively separates anxiety-reducing properties from those producing undesired psychological side effects does not yet exist. There are a variety of drugs of several chemical classes which approximate these criteria, however: bromides, paraldehyde, chloral hydrate; the newer minor tranquilizers such as meprobamate (Miltown*), diazepam (Valium*), and chlordiazepoxide (Librium*) and assorted other compounds (e.g., ethchlorvynol, glutethimide) which do not fall into a neat chemical classification. Alcohol and barbiturates are also often considered with the anxiolytic sedatives, although we will keep them separate in the following discussions since they have already been covered in previous sections of this report.

77. Most minor tranquilizers fall between alcohol and barbiturates in sedative action at a therapeutic dose. The disparate classes of chemicals have generally similar physiological action and will be treated as a group, with individual differences sometimes characterized. The minor tranquilizers have tended to replace barbiturates as day-time sedatives in recent years. These drugs and other sedatives are commonly referred to as 'downers' in the drug argot.

In Canada and the U.S.A., well over $500 million is spent each year on sedative drugs, to treat a wide variety of symptoms falling under the category of anixety.131 Although there are no statistics available to us at this time on the Canadian imports, exports, manufacture, production or sale of minor tranquilizers, many observers feel that the supply greatly exceeds medical needs. The distribution route which the drugs follow after production is not known, and a considerable percentage may be diverted for non-medical use. Clandestine manufacture of minor tranquilizers does not appear to occur and all such drugs initially start into the market as lawful materials. As described in the section on barbiturates, patients may be able to procure large quantities of these drugs through legitimate prescription channels.
79. In the U.S., production figures for tranquillizers exceed those for 'sleeping pills', 'pep pills', and opiate narcotics combined. In additional,

In 1965 in the U.S.A., some 58 million new prescriptions and 108 million refills were written for psychotropes (sedatives, tranquillizers and stimulants) and these 166 million prescriptions accounted for 14% of the total prescriptions of all kinds written in the United States.

79. Minor tranquillizers are so widely prescribed that the American Medical Association warned doctors about overprescription and outlined ways in which the 'misuse of sedatives' by 'the prolonged and unsupervised administration of (tranquillizers) for symptomatic relief often without adequate diagnosis or knowledge of the patient's past experience with medications, or attitudes towards drugs' is aggravated. Evidence in these recent U.S. surveys indicates that the minor tranquillizers and other sedatives are more commonly used than the stimulants among respondents above age 20.

The minor tranquillizers, along with barbiturates, tobacco, and alcohol, are among the most widely used drugs in North American society, and are the toxic agents in a large number of poisoning cases. Since chronic tranquilizer dependence may be quite frequent, and may involve considerable impairment, the public's relative indifference to the hazards of tranquilizer pill-popping is quite alarming. As in the case of alcohol and barbiturates, much research on medical use has been done, but little investigation of non-medical use of tranquillizers has been carried out.

Medical Use

80. Minor tranquillizers are widely used in medical practice today, and are mainly prescribed for patients suffering from anxiety, tension, behavioural excitement and insomnia. They are also used in the treatment of lower back pain, convulsive disorders and withdrawal symptoms of opiate narcotic and alcohol dependence.

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

Administration, Absorption, Distribution and Physiological Fate
81. Minor tranquillizers are usually administered orally as elixirs or tablets, but are also sometimes injected, for both medical and non-medical purposes. They are generally rapidly absorbed by the stomach, intestine and rectum, and the absorption is most rapid with an empty stomach. Once absorbed, the drugs are distributed quite uniformly throughout the body, with the latency of response dependent on the particular chemical class. Some are metabolized, or otherwise chemically altered (usually in the liver), and excreted into the urine, while others are eliminated unchanged. The factors of distribution, metabolism, and excretion, are primarily responsible for differences in potency and duration of action of the different minor tranquillizers. The detection of some acute and chronic tranquillizer use is not easy, and the methods of detection of the metabolites in urine are highly sophisticated and expensive.

**Psychological Effects**

82. Many of the psychological effects of minor tranquillizers are similar to those observed with alcohol and barbiturates. As with these other sedatives, psychological and behavioural responses to low doses of minor tranquillizers are quite variable. There may be a sedation in some instances and, in others, an increase in activity. Studies reveal that complex interactions between the type of drug and the level of anxiety occur, even within the same pharmacological group; the drugs may impair or improve performance, depending on dose and the degree of anxiety present.131

Normal doses usually provide relaxation, a feeling of well-being and perhaps some loss of inhibition. With excessive use of these drugs the following effects may be observed; disorientation, confusion, memory impairment, trance-like episodes, double vision, personality alterations, rage reactions and other symptoms resembling those of drunkenness. Such manifestations are difficult to differentiate from the inebriation caused by barbiturates and alcohol.

83. It appears that driving skills may not be impaired at clinical doses, so long as the user is not already drowsy or has not taken other sedatives such as alcohol. At higher doses, driving skills are more likely to be seriously impaired. One report states that the accident rate in a group of drivers using prescribed doses of Librium* was 10 times the general accident rate for New York State, but it is not clear whether the accident rate among these drivers who 'needed' a tranquillizer, was so high because of, or in spite of, the drug they were taking.167 In Canada it is an offence to drive under the influence of drugs, and the penalties are similar to those for drunken driving, although convictions involving tranquillizers are rarely reported.

**Physiological Effects**
84. The response to moderate and high doses of minor tranquillizers is a general depression of nervous and muscular activity and several other bodily functions. Compared with other sedatives, the newer minor tranquillizers may 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. The minor tranquillizers affect the levels of some neurohumors in the brain which may be involved in the tension-anxiety states. However, the exact mechanism by which these drugs produce their effects is unknown.

Side effects observed with these drugs include drowsiness, ataxia, lethargy, skin rashes, nausea, diminished sex interest, menstrual and ovulatory irregularities, blood abnormalities and increased sensitivity to alcohol. High doses may depress respiration, produce unconsciousness and coma and can produce death. There is no clear evidence of permanent irreversible damage to neurological or other physiological processes even with long-term non-medical use. The fact that chronic users of minor tranquillizers maintain a reasonable diet and are not reported to suffer from malnutrition, may account for some of the differences between the chronic effects of tranquillizer use and alcoholism.

**Tolerance and Dependence**

85. Tolerance usually develops to most of the effects of the minor tranquillizers on repeated use and the dose must often be increased in order to obtain the desired effects. No tolerance develops to the lethal toxicity, however, and chronic users must be especially attentive to the quantities consumed. With one or two exceptions, these drugs have been reported to produce both psychological and physiological dependence, resembling that seen with alcohol and the barbiturates.

The clinical descriptions of the abstinence syndrome, reported to follow abrupt withdrawal, after excessive dosages of the minor tranquillizers, indicate a marked similarity to one another and to alcohol and barbiturates. The syndrome may be characterized by anxiety, apprehension, tremulousness, muscle twitches, insomnia, headache, fever, loss of appetite, nausea, vomit, abdominal cramps, sweating, tachycardia, fainting, hyperactive reflexes, convulsions, and uncontrolled urination and defecation. In addition, delirious states can occur with motor agitation, hallucinations, delusions, disorientation and confusion. The abstinence syndrome can be very serious, and deaths have been attributed to withdrawal of meprobamate (Miltown*) and methyprylon (Noludar*).72

**Minor Tranquillizers and Other Drugs**
1. Cross-tolerance and cross-dependence exist among the minor tranquilizers and with other sedative drugs. This cross-tolerance does not appear to affect the lethal dose and, consequently, alcohol or barbiturates taken simultaneously with large quantities of minor tranquilizers may act additively and produce toxic or fatal reactions. Heavy users of these drugs may switch among the sedatives, if necessary or convenient, and alcoholics often use barbiturates and tranquilizers to sustain inebriation. Individuals dependent on opiate narcotics often also use large quantities of minor tranquilizers.