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Abuse Liability of Benzodiazepines

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I. Introduction

BENZODIAZEPINES now occupy a prominent place in therapy for anxiety, insomnia, and numerous physical diseases, especially disorders of the circulatory and musculoskeletal systems. Since these are among the most widely prevalent psychiatric and medical disorders, use of the benzodiazepines† has become quite extensive in most populations served by effective health care.

The widespread use of these compounds has, perhaps inevitably, provoked considerable concern in some quarters. Much of this concern has focused on the benzodiazepines' liability for abuse. Rational assessment of the abuse liability of drugs should consider the evidence in a broad context, weighing this risk against the benefits of the drugs' use. Because of the attention that has been devoted to the extensive use of the benzodiazepines, more information may be available on the actual use of these drugs than of any other group of drugs acting on the central nervous system (CNS). We felt it should be possible to take advantage of this extensive information to address the full scope of concerns relevant to the benzodiazepines' abuse liability as broadly conceived, i.e., as relevant to public health and policy concerns.

We define the *abuse liability* of a compound as its capacity to produce psychological dependence (which we prefer to address in terms of objective measures of drug taking), or physiological dependence, in conjunction with the capacity to alter behavior in a manner that is detrimental to the individual or his social environment. This definition is consistent with the broad conception of abuse liability under which psychotropic substances are reviewed by the World Health Organization (1174). In accord with this definition, this review includes consideration of the areas of research described below.

Section II considers studies in animals and humans of drug taking and drug seeking. We consider the analysis of these behaviors to be of fundamental importance to abuse liability assessment.

Physiological dependence is sometimes associated with the chronic administration of drugs, in the context of therapeutic use or of misuse. Section III therefore considers research in animals and humans pertaining to the potential of the benzodiazepines to produce physiological dependence, in that this information might bear on their liability for abuse.

Section IV reviews evidence pertaining to the adverse behavioral consequences of benzodiazepine use, including experimental research into effects on human cognition and performance (but excluding, perhaps arbitrarily, evidence from animal research that could be construed as relevant to behavioral toxicity), and including epidemiological data bearing on the contribution of these effects to automobile and other accidents.

† A large number of substances that contain a benzodiazepine chemical structure have been synthesized. Two helpful sources of information on the chemistry, biochemistry, and pharmacology of these substances are those by Schütz (988) and Haefely et al. (416).

Section V considers epidemiological research pertaining to the use and misuse of the benzodiazepines. Information on the actual use of these drugs provides an essential context in which to evaluate the significance of evidence of their liability for abuse. This evaluative context is further enhanced by epidemiological data on misuse of the benzodiazepines and of the consequences of such misuse; these data also represent potential reference points for assessment of the experimental research on abuse liability.

Section VI presents a general summary and discussion of the review findings and of the implications of these findings with respect to research, clinical practice, and public health and policy concerns.

II. Studies of Drug Taking and Drug Seeking

A. Introduction

The ability of a drug to reinforce drug-taking behavior is an essential determinant of its liability for abuse. Reinforcement is a process in which the probability that a particular behavior will occur is increased or maintained by a stimulus that follows the behavior. Behaviors as diverse as attending cocktail parties, visiting a physician, or, in experimental studies, pressing a lever, if they result in drug administration and, as a consequence, are increased in frequency, can be said to have been reinforced by the drug. The conceptualization of drugs as reinforcing stimuli has supplanted much of what had been traditionally subsumed under the concept of psychological dependence. Often the term "psychological dependence" (or "psychic dependence") has been used to denote a condition characterized by craving for a drug or drug effect which in turn fulfills some psychological need of the individual. For example, evaluations of the liability of drugs to promote psychological dependence have often considered evidence pertaining to subjective drug effects, i.e., any private events that a subject reports in association with use of a drug. However, similar subjective effects might be reported by two individuals, of whom one is a drug abuser and the other is not; moreover, similar subjective effects may be produced by two drugs, of which one is abused and the other is not. It is inappropriate to assume that the subjective effects that may be reported following drug administration are the "reason" the subject takes the drug. Consequently, when we refer to psychological dependence, we mean this to pertain solely to the reinforcing potential of drugs, i.e., their potential to increase or maintain the frequency of the behaviors of drug seeking or drug taking.

With laboratory animals, it is relatively easy to evaluate the rate at which behaviors maintained by drug administration occur. A large number of experiments have studied the rate at which a relatively well-defined behavior, such as pressing a response key, is maintained

by drug administration in animal subjects, and studies such as these have become commonplace in preclinical evaluation of the likelihood of abuse of behaviorally active drugs (1172, 986). Most of these studies have examined behavior maintained by i.v. drug administration; however, since benzodiazepines are typically administered p.o., there has also been some interest in assessment of the reinforcing effects of these drugs when taken p.o. or intragastrically (i.g.) by the subject. These behaviors in animals are relatively free of confounding problems, such as social effects, that may complicate studies in humans.

Griffiths and Ator (390) provided a useful review of experimental assessment of benzodiazepine abuse liability. More recently, these authors and their colleagues (396) published an assessment of a single benzodiazepine, triazolam, that took an approach similar to that of the present review.

B. Studies in Animals

The studies covered in this section have all examined conditions in which experimental subjects take drugs in some manner. In some studies subjects ingest the drug p.o. In these studies the reinforcing effects of the drugs are often assessed in tests of "preference"; drug is made available in a solution or in food (vehicle), vehicle is made available without drug, and the amounts of drug ingested are compared to the amounts of vehicle ingested. In other studies the drug is delivered, i.v. or i.g. through a chronic indwelling catheter, contingent on some easily recorded response such as pressing a lever; reinforcing effects of the drug are assessed by determining if the rate of response when drug is administered is greater than the rate of response when vehicle is administered.

1. Studies of oral drug ingestion. Several studies have examined whether subjects ingest more drug solution when either diazepam or chlordiazepoxide solutions and vehicle solutions are continuously available; the subjects did not ingest more drug than vehicle (14, 433, 566, 1203). In one study, greater intake of diazepam developed in 9 of 20 rats exposed to diazepam and vehicle (324). These rats consumed up to 82% of their daily fluid as diazepam (0.1 mg/ml), resulting in an intake of 13 mg/kg. The remaining 11 rats consumed from 20 to 50% of their daily fluid as diazepam. Since large differences in intake of drug solution over vehicle do not develop when subjects are simply exposed to benzodiazepine solutions, techniques have been developed in the attempt to induce greater drug intake. Several studies have exposed subjects to a condition in which the only fluid (433, 1051) or food (1203) available had drug added. None of those studies showed the development of a preference for drug solution or food mixed with drug following periods of forced consumption of either chlordiazepoxide (433, 1051) or diazepam (1203). Although substantial drug preferences were not established in these studies, a certain amount of drug intake was maintained even when drug-free food or water was concurrently available. Amounts of drug orally ingested in "choice" tests have varied from about 16 mg/kg (433) to about 43 mg/kg chlordiazepoxide (1051; assuming rats weighed 300 g) and about 40 mg/kg diazepam (1203).

Other investigators have deprived subjects of fluid for a day and then allowed access to a drug solution. Using this technique, and adding flavoring to mask the bitter taste of a diazepam solution, intake was not above control levels (1128). A similar study of chlordiazepoxide intake in which no attempt was made to mask the taste of the drug solution found a progressive decrease in consumption over 3 days (1168).

More exotic techniques have also been applied in an effort to induce benzodiazepine intake. Several studies have suggested that electrical stimulation of the lateral hypothalamus induces significant ethanol consumption (15, 1130). This technique was ineffective, however, in inducing consumption of diazepam solutions (14). "Stressful" conditions, produced by either avoidable or unavoidable painful electric shock, likewise produced no significant consumption of a chlordiazepoxide solution (566).

When small amounts of food are presented intermittently, large amounts of fluid consumption can be induced (schedule-induced polydipsia); this technique has been used successfully in the past to induce consumption of amounts of ethanol sufficient to produce physiological dependence (283). Sanger (970) compared schedule-induced drinking of water with schedule-induced drinking of chlordiazepoxide solutions (0.1 or 0.4 mg/ml). The largest volume intake occurred in the group of subjects exposed to the lower concentration of chlordiazepoxide; the least was in the group exposed to the higher concentration. Although Griffiths and Ator (390) suggested that the lower concentration of chlordiazepoxide may have functioned as a reinforcer in this circumstance, Marks (714) noted that another interpretation is possible. One direct effect of chlordiazepoxide is an increase in fluid intake. Indeed, when Sanger administered chlordiazepoxide before experimental sessions to the group of subjects exposed to water, fluid intake was increased. Thus, the elevated intake in the group of subjects exposed to the low chlordiazepoxide solution may have been due to the facilitation of drinking produced by the drug, and not a reinforcing effect of the drug. Moreover, Jacquet and Stokes (519) have reported that schedule-induced chlordiazepoxide ingestion was insufficient to induce significant chlordiazepoxide preference over water.

In a study of schedule-induced midazolam intake (284), the ingested amounts of water and midazolam solution (0.05 mg/ml) were similar when food pellets were delivered once each minute during 3-h experimental sessions. During single-session probes at lower rates of pellet delivery, midazolam intake was greater than water intake. In test sessions with both water and midazolam available, there was a greater intake of midazolam solu-

tion at some but not all of the rates of pellet delivery studied. In contrast to results with chlordiazepoxide (e.g., ref. 970), this study found no direct effect of midazolam on fluid intake. Thus, the increases in intake of midazolam over vehicle under particular conditions may reflect a reinforcing effect of the drug. Additionally, further studies in these subjects suggested that some dependence had developed to midazolam, as evidenced by seizures and running fits induced by an auditory stimulus.

Harris et al. (433) used an innovative technique for establishing significant chlordiazepoxide intake. Food-deprived rats were trained with food reinforcement to lick a tube containing a drug solution. Following 25 days of training, the subjects were tested for drug or water preference for 21 days. During the test period, subjects trained with chlordiazepoxide averaged about 40% of their fluid intake as chlordiazepoxide (0.5 mg/ml). Subjects trained with meprobamate averaged about 60% of their fluid intake as meprobamate (6.0 mg/ml). These amounts resulted in intakes of about 33 and 600 mg/kg of chlordiazepoxide and meprobamate, respectively, and were about 3 times higher than intakes of subjects forced to drink drug solutions by allowing access only to the drug solutions for comparable time periods.

Recently, Ator and Griffiths (28, described in ref. 396) presented a preliminary report of a complex procedure for establishing oral intake of triazolam in baboons. The procedure follows those developed by Meisch (750) for studying ethanol drinking. In the Ator and Griffiths study, two baboons were fed only during 3-h experimental sessions in which a single bottle of triazolam solution was available to the subject; water was available at all other times. Through feeding, the subject was induced to drink the drug solution and, after some exposure, food was no longer necessary to maintain drinking. Over a period of several weeks, the concentration of the drug solution was gradually increased; each increment was made only after total fluid intake had stabilized. During the last several days of exposure to each concentration, the subject was tested for preference for vehicle over drug solution by exposing the subject to two bottles, in randomized positions, one containing drug and the other vehicle. Although the volume of drug solution consumed prior to preference tests was reported to be unrelated to triazolam concentration, and therefore presumably not different from vehicle amounts, a preference test in each of the two subjects found a greater volume of drug solution ingested at one of the seven concentrations studied. However, under this procedure, preferences for methohexital were larger and occurred over a wider range of doses (29). In a second part of the study of triazolam, subjects were required to press a response key in order to make the drug available. The number of responses required per triazolam drink was increased until responding ceased. Under this procedure, triazolam was not different from vehicle in maintaining key-press responding. In further studies with these subjects, the benzodiazepine antagonist flumazenil (Ro 15-1788, previously designated as flumazepil) precipitated withdrawal signs, indicating that the intake of the drug was sufficient to produce some physiological dependence.

In summary, none of the studies of oral benzodiazepine intake have shown a substantial preference for drug solution over vehicle. Some of the studies have failed to find appreciable drug intake (e.g., refs. 14 and 566). Several others (e.g., refs. 433, 970, 1051, and 1203), while not showing drug preference, have indicated that consumption of intoxicating amounts can be induced. Finally, others have suggested that, under some conditions, it is possible to induce consumption of amounts sufficient to produce physiological dependence (28, 284).

2. Studies of place preference. In studies of place preference, subjects are placed in a chamber with two compartments. During training, the subject is placed in one compartment, depending on whether it has been injected with drug or with vehicle, with no access to the alternate compartment. After some exposure to both drug and vehicle, the subject is then placed in the chamber and given free access to either compartment. The time spent in the compartment previously associated with drug is considered an indication of the reinforcing effects of the drug. Presumably the stimulus conditions in the compartment associated with drug develop conditioned reinforcing effects, and the movement of the subject to the drug-associated side is reinforced by those stimuli. In a place-preference study of diazepam (1032), a dose-dependent place preference was observed with a maximal effect obtained at 1.0 mg/kg (i.p.). Place preference did not develop when the benzodiazepine antagonist CGS-8216 was administered with diazepam. This finding of place preference induced by diazepam is of interest, and further studies comparing the procedure with others used for assessing reinforcing effects of drugs would be of value.

3. Drug infusion studies. Many different procedures have been used in studying drug self-administration. In the simplest of these, every response the subject makes, at any time of day, produces a drug infusion. This procedure can be designated as fixed-ratio one-response (FR 1) with unlimited access to the drug. Other procedures involve scheduling infusions to follow only some of the responses, according to some preprogrammed ratio of responses to injections, e.g., ten responses per injection; this schedule can be designated a fixed-ratio ten-response (FR 10) schedule. Additionally, the access to the drug may be limited to certain time periods during the day. For example, a drug may be available only during a 2-h experimental session. Although more complex schedules of drug availability have been devised, only a few have been used in studying benzodiazepine self-administration.

On surface, the FR 1 schedule with unlimited drug

access appears to be a simple, unambiguous, and easily interpreted procedure. In interpreting these studies, however, care must be exercised, since under these conditions, responding may be poorly maintained, whereas under others responding may be maintained at much higher rates; see Kelleher (571) for a discussion.

a. STUDIES IN RATS. Using an FR 1 schedule of continuous access to i.v. drug, Collins et al. (188) found that diazepam (0.1 and 0.01 mg/kg/injection) maintained responding in one of seven rats studied. In contrast, flurazepam maintained responding in four of six rats tested at doses of either 0.32 or 0.032 mg/kg. Replications of these doses in other groups of subjects did not produce the same incidence of reinforcing effects. However, this study indicated that, under some conditions, a reinforcing effect of flurazepam can be obtained in rats.

Naruse and Asami (803) studied responding maintained by i.v. diazepam in rats with and without a history of forced exposure to the drug. Diazepam maintained responding at rates greater than those maintained by vehicle in both groups. The doses studied in different groups of subjects were 0.5, 1.0, and 2.0 mg/kg/injection. Rates of responding at the lowest dose were not greater than those obtained with vehicle alone until after the 13th day of exposure. Rates of responding increased at the highest rate in subjects receiving the highest dose per injection; however, asymptotic rates obtained in each of the higher-dose groups were comparable and greater than those obtained in the lower-dose group. In contrast, a group of subjects studied with morphine (0.5 mg/kg/injection) showed higher rates of responding and no evidence of reaching an asymptote over a 30-day period.

Pilotto et al. (872) used a technique similar to schedule-induced polydipsia in order to establish i.v. self-administration of diazepam. In that procedure, food pellets were delivered to the subjects independently of behavior at a rate of once per minute; key-press responses produced i.v. injections via a jugular catheter. Diazepam maintained responding at rates greater than those maintained by vehicle; and rates of responding were dose-dependent, with the lowest dose per injection maintaining the highest response rates. The intake of diazepam for the entire 1-h session ranged from about 2 mg/kg, at the highest dose, to about 1 mg/kg at the lowest dose. Response rates were appreciably lower in subjects that were not exposed to the schedule of food delivery.

There are few reports of responding maintained by i.v. injection of benzodiazepines other than those pertaining to the effects of diazepam in rats. In one published abstract (300), a dose of approximately 0.17 mg/kg of midazolam (assuming rats weighed 300 g) maintained responding during unlimited access conditions. Responding reportedly decreased when saline was substituted for drug. In another abstract with few procedural details (219), i.v. chlordiazepoxide was reported to maintain responding during eight daily 10-h sessions.

There has been only one full report of i.g. self-administration of a benzodiazepine other than chlordiazepoxide in rats. Gotestam (374) reported medazepam maintained responding above saline or vehicle rates at doses of 2.5, 5.0, and especially 10.0 mg/kg. At 10.0 mg/kg, responding was maintained above vehicle rates in five of seven rats. Davis et al. (219) also reported i.g. chlordiazepoxide maintained responding.

b. STUDIES IN NONHUMAN PRIMATES. **i. Continuous access to intragastric drug injection.** Several studies, of which the reports were lacking in procedural details (in particular regarding the doses studied), have indicated that diazepam does not maintain responding when administered i.g. (12, 1131). However, there are more detailed reports on responding maintained by i.g. diazepam. Yanagita and colleagues (1185, 1179, 1181) showed marginal self-administration of diazepam under FR 1 schedules with unlimited access. In one study (1185, 1179), a dose of 0.25 mg/kg/injection produced small increases in rates of responding in two of four monkeys. At a dose of 1.0 mg/kg/injection, responding was maintained above the original vehicle rates in only one of four subjects. A return to vehicle injections for 3 days showed rates of responding higher than those originally maintained by vehicle in two of the four subjects. Further studies of diazepam self-administration at doses of 1.0 and 2.0 mg/kg/injection generally failed to show rates of responding appreciably greater than those maintained by vehicle alone at the second determination. A final return to vehicle for 1 wk generally resulted in rates of responding that were comparable to those maintained by vehicle at the second determination. These results indicate that i.g. diazepam can maintain responding at rates greater than those initially maintained by vehicle, but that these rates are generally low. They also make the point that repeated evaluation of rates of responding maintained by vehicle is necessary in order to determine whether the drug is actually maintaining responding.

Altshuler and Phillips (12) reported that i.g. chlordiazepoxide did not maintain responding. In contrast, Yanagita and Takahashi (1195) reported that i.g. chlordiazepoxide maintained responding at a dose of 10.0 mg/kg/injection in two monkeys with a history of i.v. *l*-1,2-diphenyl-dimethyl-aminoethan-HCl (SPA) self-administration. Responding was maintained for longer than 8 wk during which time the average daily intake was about 100.0 mg/kg.

Studies of self-administration of a number of other benzodiazepines have been conducted by Yanagita and colleagues; and most of these results have been recently reviewed (1178). Triazolam at doses of 0.015 to 0.25 mg/kg/injection (1187), clobazam at doses of 0.25 to 2.0 mg/kg/injection (1202), and flutoprazepam (KB-509) at doses of 0.015 to 0.06 mg/kg/injection (1189) appeared to maintain responding to a greater extent than the other benzodiazepines studied by Yanagita and colleagues.

These drugs maintained responding at rates above those maintained by vehicle in three of the four subjects tested. Lorazepam at doses of 1.0 to 2.5 mg/kg/injection (1198) and alprazolam at doses of 0.0075 to 0.03 mg/kg/injection (1201) maintained responding in two of four subjects with experience in drug self-administration procedures. In a subsequent study (1183), lorazepam marginally maintained responding in only one of three subjects.

Several other benzodiazepines failed to maintain responding consistently. Studies of i.g. self-administration of flunitrazepam showed rates of responding greater than those maintained by vehicle in two of four monkeys at a dose of either 0.25 or 0.06 mg/kg/injection (1184), whereas lormetazepam maintained responding at rates greater than those maintained with vehicle in two of five subjects at doses of 4.0 to 16.0 mg/kg/injection (1183). In each of the above studies, rates of responding maintained by drug were typically only slightly above those maintained by vehicle. Nitrazepam maintained responding in one of four monkeys at a dose of 1.0 mg/kg/injection (1199). Two of the subjects were tested only at a 5.0-mg/kg dose. A later report (1181) indicated that nitrazepam maintained responding in two of four subjects. Intragastric oxazolam (10.0 mg/kg) was reported to maintain responding in two of four rhesus monkeys; however, "neither of them showed a high intake or any noteworthy drug effects" (1195). One of four monkeys was reported to self-administer fludiazepam at a dose of 1.0 mg/kg/injection. After 4 wk of exposure, this monkey self-administered about ten daily doses of 1.0 mg/kg, which was reported to be slightly greater than control levels. The remaining three monkeys did not show any drug self-administration (1186).

Studies of i.g. halazepam self-administration were reported by Yanagita et al. (1192). In this report, rates of responding maintained by water were lower at the second observation than the first; however, the vehicle used with halazepam was not studied. In three of four subjects a dose of 5.0 mg/kg maintained responding at rates greater than those maintained by water. Yanagita et al. (1192) concluded that the reinforcing potency of halazepam is lower than or at most equal to that of diazepam and chlordiazepoxide and that the reinforcing effect was "positive but weak." In a subsequent report (1181), halazepam was compared to quazepam as well as diazepam and nitrazepam. In that study, both halazepam and quazepam were reported to maintain responding in one of four subjects studied, whereas the other drugs were reported to maintain responding in two of four subjects.

Neither nimetazepam (methylnitrazepam, S-1530) at doses of 1.0 or 5.0 mg/kg/injection (1199) nor haloxazolazepam (CS-430) at doses of 0.5 or 2.0 mg/kg/injection (1193) maintained responding in any of the four subjects tested with each of these drugs. Cloxazolazepam at doses from 1.0 to 10.0 mg/kg/injection (1197), estazolam at doses of 1.0 and 5.0 mg/kg/injection (1200), prazepam at doses of 0.25 and 1.0 mg/kg/injection (1196), ethyl loflazepate (CM 6912) at doses of 0.015 to 0.25 mg/kg/injection (1182), mexazolam at doses of 0.2 to 5.0 mg/kg/injection (1180), and clonazepam at doses of 0.125 and 0.25 mg/kg/injection (1190) were among the drugs that did not maintain responding reliably in any subjects either before or after forced exposure to the drug.

ii. Continuous access to intravenous drug injection. Reinforcing effects of several benzodiazepines have been evaluated using the i.v. route of administration in monkeys. Studies of diazepam self-administration under conditions of unlimited access have yielded inconsistent results that are not always easily interpreted and will consequently be considered in some detail. An initial study of diazepam self-administration under conditions of unlimited access indicated that diazepam at a dose of 0.4 mg/kg/injection maintained responding above vehicle rates (1195). In that study, diazepam maintained responding in three of four experimentally naive monkeys, and the average daily dose administered was from 8 to 10 mg/kg. Similarly, chlordiazepoxide maintained responding in three of four naive subjects at a unit dose of 1.0 mg/kg/injection, yielding a daily intake of 10 to 20 mg/kg. In these subjects the rate of responding decreased to low rates after about 4 wk of exposure to the drug. In this study, concerned primarily with whether acquisition of responding would occur with the drugs, there was no attempt to determine dose-effect relations nor whether response rates would return to low levels when vehicle was substituted for drug. In a further report (1191), three of five experienced subjects showed increased rates of responding when diazepam (0.4 or 1.0 mg/kg/injection) was available. A fourth subject started to respond after a 4-wk period of forced exposure to the drug (6.0 mg/kg/day), whereas this treatment did not induce responding in the fifth subject. When saline was substituted for diazepam, response rates decreased to lower levels in three of the four subjects whose responding was maintained by drug.

Responding maintained by the nonbenzodiazepine, zopiclone, has also been reported under conditions of unlimited access in four subjects (1185, 1179). In that study, responding was maintained in both experimentally naive and experienced subjects at doses of either 0.25 or 1.0 mg/kg/injection, depending on the subject. Rates of responding maintained by drug were clearly above rates of responding maintained by vehicle.

In contrast to these results, Yanagita and colleagues (1188) found that responding was maintained only marginally in two of four subjects given dipotassium clorazepate (0.25 and 1.0 mg/kg/injection). In one subject with a history of drug self-administration, responding was maintained by clorazepate only after a 2-wk forced exposure to the drug (12.0 mg/kg/day). In another experienced subject, responding was not reliably maintained. In two experimentally naive subjects, responding was poorly maintained if at all.

Kubota et al. (615) trained cynomolgus monkeys under

an FR 1 schedule of pentobarbital injection and substituted various doses of triazolam, midazolam, chlordiazepoxide, and flurazepam. Both triazolam (0.001 to 0.03 mg/kg/injection) and midazolam (0.01 to 0.03 mg/kg/injection) maintained responding in all of the subjects studied, and rates of responding were comparable to those maintained by pentobarbital. Chlordiazepoxide (0.1 to 1.0 mg/kg/injection, depending on the subject) maintained responding in three of five subjects studied, although not at rates comparable to those maintained by pentobarbital. Flurazepam (1.0 and 3.0 mg/kg/injection) did not maintain responding in any of the subjects studied. The investigators also studied acquisition of responding in subjects that had not received preliminary training with pentobarbital; responding was maintained by midazolam (0.03 or 0.1 mg/kg/injection) in three of four such subjects, and by triazolam (0.003 or 0.01 mg/kg/injection) in two of four. Pentobarbital maintained responding in three of four experimentally naive subjects.

iii. Intermittent drug availability. In most of the studies described above, drug was available for each response 24 h per day. In the studies described in this section, access to drug was typically limited to defined experimental sessions lasting several hours per day, and response requirements were greater than one response per injection. Under these conditions, there is some opportunity for drug administered in one experimental session to be metabolized before the next session, limiting the influence of effects of previously injected drug on the likelihood of subsequent responding.

Several studies have examined benzodiazepine self-administration when more than one response was required for each i.v. injection. In one study (413), responding of rhesus monkeys trained on an FR 2 schedule of codeine injection was not maintained when diazepam (0.05 to 4.0 mg/kg/injection) was substituted for codeine. A study reported by Hoffmeister (482) is lacking procedural details; however, self-administration was established in rhesus monkeys with codeine under a schedule that appears to have been an FR 10 schedule. Sessions were apparently 3 h in length. Different doses of diazepam (0.005 to 0.5 mg/kg/injection) were substituted for the usual codeine over several successive sessions. Although data from saline controls were presented, the vehicle used for diazepam was not specified, and no data for vehicles other than saline were presented. Doses of 0.005 to 0.05 mg/kg/injection maintained responding at rates above those maintained by saline, with a maximum at 0.05 mg/kg/injection, which was about half the rate maintained by codeine. A higher dose (0.5 mg/kg/injection) did not maintain responding at rates greater than those maintained by saline.

Bergman and Johanson (64) studied diazepam self-administration under several procedures. Rhesus monkeys were trained under FR 10 schedules of cocaine or pentobarbital injection during sessions lasting 1 to 3 h. Diazepam doses were periodically substituted for the training drug for several consecutive sessions. In 4 of 11 subjects trained with cocaine, diazepam maintained rates of responding above vehicle rates; in three of these subjects, the rates of responding maintained by diazepam were substantially greater than those maintained by vehicle. Under an FR 1 schedule, diazepam did not maintain rates of responding above vehicle rates in any of the subjects tested. When diazepam was substituted for pentobarbital, responding was maintained in all four monkeys studied, and in two of the subjects responding was maintained at rates substantially higher than those maintained by vehicle. The authors concluded that the reinforcing effects of diazepam may depend upon the conditions in which it is studied, and that an important condition appeared to be the history of the subject. Thus, for subjects with a history of cocaine-maintained behavior, diazepam appeared to have only marginal reinforcing effects, whereas for subjects with a history of pentobarbital-maintained responding, diazepam appeared to be more likely to maintain behavior.

In other studies from the same laboratory, Johanson (534) has reported that i.v. injection of flurazepam (0.01 to 1.0 mg/kg/injection), lorazepam (0.01 to 1.0 mg/kg/injection), and estazolam (0.003 to 0.03 mg/kg/injection) maintained responding under a fixed ratio 10-response schedule when substituted for pentobarbital. Flurazepam maintained responding at rates above those maintained by vehicle in all of the six subjects studied, whereas lorazepam and estazolam maintained responding above vehicle rates in four of five or six subjects studied, respectively. In a subsequent study (535), some of the effects of lorazepam and flurazepam, but not pentobarbital, were antagonized by flumazenil.

Using a cocaine-substitution procedure similar to that used by Johanson and colleagues, Balster and Woolverton (38) found that neither chlordiazepoxide (0.03 to 1.0 mg/kg/injection) nor clorazepate (0.03 to 1.0 mg/kg/injection) maintained responding at rates above that maintained by vehicle. Kubota et al. (615) substituted midazolam and triazolam for pentobarbital in cynomolgus monkeys trained under FR 10 schedules of pentobarbital injection. Midazolam (0.003 to 0.1 mg/kg/injection) and triazolam (0.001 to 0.03 mg/kg/injection) maintained responding at rates comparable to those maintained by pentobarbital.

Self-administration of a series of six benzodiazepines was studied by Griffiths et al. (397) and compared to self-administration of several barbiturates. Baboons were trained to respond 160 times (FR 160) for injections of cocaine. A 3-h timeout period followed each injection, and subjects were studied 24 h per day. Once responding was established with cocaine, the other drugs were substituted for cocaine for periods of 12 to 15 days. The three barbiturates studied, amobarbital, pentobarbital, and secobarbital, all maintained high rates of responding that approached one response per second and were comparable to rates of responding maintained by cocaine.

Rates of responding maintained by the benzodiazepines were generally lower. Diazepam, at doses of 0.03 to 1.0 mg/kg/injection, maintained response rates marginally above those maintained by vehicle. Clonazepam (at doses of 0.01 to 1.0 mg/kg/injection) and flurazepam (at doses of 1.0 to 10.0 mg/kg/injection) also maintained response rates above vehicle rates. The highest rates of responding were maintained by midazolam; these rates approached those maintained by cocaine and were above those maintained by vehicle at doses of 1.0 to 10.0 mg/kg/injection. Clorazepate (0.01 to 5.6 mg/kg/injection; the drug being probably hydrolyzed to desmethyldiazepam in solution prior to injection) and medazepam (0.01 to 10.0 mg/kg/injection) failed to maintain response rates significantly greater than those maintained by vehicle. With the exception of midazolam, all of the benzodiazepines studied maintained maximal rates of responding between 0.01 and 0.03 response per second. Rates of responding maintained by vehicle were typically between 0.003 and 0.01 response per second.

Griffiths et al. (397) also presented data on the average number of injections taken per day, a measure that can roughly correspond with response rates under the conditions of this particular procedure. With all of the benzodiazepines studied, the average number of injections per day was greater for drug than for vehicle at some dose in most of the baboons tested. As expected from the data on response rate, with midazolam the mean number of injections taken per day approached eight, the maximum possible and the level achieved with cocaine and the barbiturates studied. Using the same procedure as that used by Griffiths et al. (397), Lukas and Griffiths (682, reported in ref. 396) reported that triazolam maintained higher rates of self-injection than did diazepam. The maximum number of triazolam injections per day approached that observed when cocaine maintained responding and was greater than that observed in the previous study (397), when diazepam maintained responding.

Under progressive ratio schedules, subjects are initially trained under an FR schedule and are subsequently studied under a condition in which the response requirement is increased after each injection. The number of responses required before the subject ceases to respond is considered the breaking point of the ratio. A comparison of triazolam and midazolam indicated little difference between the breaking points for the two drugs. In comparison, pentobarbital generally maintained responding at higher ratios than did either of the benzodiazepines (615).

Findley et al. (296) studied self-administration of chlordiazepoxide in rhesus monkeys under a complex procedure. Subjects were trained under an avoidance procedure in which noxious electric shock was successfully avoided by completion of either of two FR requirements associated with lights of different colors. The subject could switch the colors and FR requirements by responding on another response key. In addition to precluding shock delivery, completion of one of the FR requirements produced a drug injection, whereas completion of the other produced a vehicle injection. Finally, avoidance trials were programmed to occur every 3 or 4 h; however, the subject could initiate trials more frequently, presumably in response to the reinforcing effect of the drug. Under these conditions, both subjects continued to avoid shock and take chlordiazepoxide injections. In further experiments, subjects were given a choice between selected doses of chlordiazepoxide and secobarbital. In general, the subjects self-administered secobarbital more than chlordiazepoxide.

4. Summary. Studies of oral benzodiazepine intake have generally failed to find substantial preferences of drug over vehicle after various procedures designed to establish drug intake. It should be noted, however, that there has been little success in establishing preferences for most of the types of drugs that have been examined under these procedures. Two studies have indicated that preference can be established with benzodiazepines. In each, preferences for drug were demonstrated in only a limited range of the conditions studied. In studies with rats under FR 1 continuous-access schedules of i.v. or i.g. benzodiazepine self-administration, under some conditions, responding was maintained by diazepam, as well as flurazepam, midazolam, and medazepam.

Studies of diazepam self-administration in rhesus monkeys in which every response at any time of day produced an i.g. injection have generally produced equivocal results. Even when diazepam was shown to maintain rates of responding above those maintained by vehicle, the differences in rate were quite small. Studies of i.g. self-administration of other benzodiazepines have indicated that triazolam, clobazam, and flutoprazepam can maintain low rates of responding in the majority of subjects studied. A wide variety of other benzodiazepines has generally been ineffective in maintaining responding.

Studies of i.v. diazepam self-administration in primates have found some indication of reinforcement when each response produced a diazepam injection; again, however, response rates were generally low. Further, these rates declined to even lower rates over the 2-wk period of drug availability. Of the other benzodiazepines studied, triazolam and midazolam maintained responding most consistently.

Studies of benzodiazepine self-administration under intermittent schedules of drug delivery have shown that, under some experimental conditions, diazepam could maintain responding at rates greater than those maintained by vehicle, although these rates were quite low and well below those maintained by reference drugs such as cocaine, codeine, or several barbiturates. Midazolam and triazolam, benzodiazepines that have relatively short durations of action, maintained responding at rates that

were higher than those maintained by diazepam and that approached those maintained by reference drugs. Additionally, under complex procedures, consistent chlordiazepoxide self-administration was established. Finally, in the single study of i.v. drug preference in monkeys, secobarbital was consistently selected over chlordiazepoxide.

C. Studies in Humans

As mentioned previously, we assume that evaluation of the reinforcing effects of drugs is fundamental to assessment of their liability for abuse. The types of procedures that have been used to evaluate reinforcing effects in humans have to some extent followed those used in animal self-administration studies. However, only a beginning has been made toward applying such procedures in the study of benzodiazepines in human subjects.

The few studies of human self-administration of benzodiazepines have focused upon drug preferences and the subjective effects of the drug ingested. These studies have been carried out in human volunteers with and without chronic anxiety, in those suffering from insomnia, and in subjects with established histories of sedative abuse. Other experiments on other patient populations (e.g., heroin abusers maintained on methadone) are probably not as relevant to the broader issues of abuse liability assessment of the benzodiazepines.

Some investigators assume that subjective reports of the effect of a drug are associated with its abuse liability (522). From our point of view, as discussed previously (page 254), no assumption of an association between subjective effects and other properties of the drugs need nor, indeed, should be made; rather, as in some of the studies described below, such effects and properties should be studied together, to examine their covariation.

Some recent publications have provided valuable reviews of experimental assessments in humans of the benzodiazepines' liability for abuse (e.g., refs. 400, 391). De Wit and Johanson (227) have reviewed problems associated with using human subjects in such assessments, including problems associated with drug preference testing and with measurement of subjective effects in general. They review studies that they and their coworkers had completed, with a view to evaluating the strengths and weaknesses of current methodology in this research. The review discusses the appropriateness of subject samples employed in these studies, and specifically questions the appropriateness of such evaluations in subjects with histories of drug abuse. The authors make the point that criteria for subject selection are important determinants of study results and that drug preferences may depend on individual variations in mood as well as on response to drug. They emphasize that a variety of environmental conditions should be evaluated, and drug preferences assessed under each, before general conclusions are drawn about such preferences.

1. Studies in normal, anxious, and insomniac subjects. In a study (536) of preference for diazepam (2, 5, or 10 mg) over placebo, for amphetamine (5 mg) over placebo, or for specific doses of diazepam (2 versus 5 mg), subjects were given color-coded capsules on four occasions and asked to fill out questions regarding mood states at 1, 3, and 6 h after drug administration. After experiencing each drug or placebo condition twice, the subjects were exposed to five sessions in which they could choose between the capsules while other conditions remained the same. In none of the comparisons was diazepam chosen in more than 50% of choice trials; in the 5- and 10-mg diazepam preference tests, placebo was chosen more often. In contrast, amphetamine was preferred significantly over placebo. Diazepam produced significant changes in mood that appeared to reflect decreases in vigor and arousal and increases in fatigue and confusion. The subjective effects were most evident at 1 h and were dose dependent.

De Wit et al. (228) reported a study applying the same procedure as described above for diazepam to the evaluation of lorazepam. They compared preference for 0.5, 1, and 2 mg of lorazepam or placebo in 12 normal subjects. No preference for drug over placebo was found; placebo was chosen more often than the two higher doses of lorazepam. Lorazepam was associated with substantial effects, similar to those described above for diazepam, both on the Profile of Mood States (POMS) and on measures from the Addiction Research Center inventory [ARCI; for a description of these measures, which are used to characterize drugs' subjective effects relative to those of drugs of known abuse potential, see Haertzen (417)]. The effects of 2 mg of lorazepam persisted for the time periods of 3 and 6 h. In a separate experiment, no preference was seen between 1 mg of lorazepam and 5 mg of diazepam.

Using a similar procedure to those described above, the same group of investigators (230) compared the effects of 15 and 30 mg of flurazepam with those of vehicle in 12 healthy male and female volunteers. The effects on choice of these doses of flurazepam related to dose in much the same way as in the studies of diazepam described above; 15 mg of flurazepam were chosen as often as placebo, whereas 30 mg were chosen significantly less than would have been dictated by chance. The lower dose produced no significant subjective effects, whereas the higher dose produced elevated sedation scores.

The studies described above indicate that it is difficult to demonstrate a preference for diazepam over placebo across subjects; a further study by this group (232) addressed the possibility that preference for diazepam might vary with individual differences in subjective response to the drug. Specifically, this study considered whether those subjects experiencing consistent subjec-

tive effects, e.g. sedation, in response to diazepam might show more or less preference for diazepam than subjects whose subjective responses were not consistent. Five- and 10-mg doses of diazepam were studied, though no results were reported for the 5-mg dose because this produced no consistent subjective effects. Subjects were divided into those who chose diazepam over placebo and those who did not. (As might have been expected based on the experiments described above, there was a significantly larger number of subjects who did not choose diazepam.) The authors could not relate subjective effects to preference for diazepam, although the "non-choosers" reported more consistent sedative responses to the drug.

In a further study of diazepam, de Wit et al. (229) examined preference for the drug in anxious subjects, thus evaluating whether the drug's reinforcing effects might be enhanced in subjects for whom it might be presumed to have therapeutic value. The subjects included normal controls and anxious subjects, some of whom were shown to satisfy DSM-III criteria (13) for generalized anxiety disorder; subjects with histories of depression or drug abuse were excluded. The drug conditions were 5 mg of diazepam, 10 mg of diazepam, or 5 mg of *dl*-amphetamine versus placebo. Procedures for drug exposure and choice trials and assessment of subjective drug effects were as described above. The anxious subjects did not choose diazepam more than placebo. There was a slight preference for placebo over 10 mg of diazepam. Though the normal subjects in this and the previous study preferred amphetamine to placebo, the anxious subjects showed no such preference. The subjective effects associated with these drug conditions in anxious subjects were much the same as described above for normal subjects. The anxious subjects reported their symptomatic status on questionnaires, confirming the diagnosis, and they also reported a significant reduction in anxiety subsequent to drug ingestion. The authors suggested that some individuals may self-administer anxiolytics as a form of self-medication; yet the present results suggest that preference for diazepam is not significantly related to presence or absence of anxiety.

Because the normal subjects in these experiments were either employed or college students, the experimenters thought that preference for diazepam might be enhanced by providing choice trials in the evening, when drug effects would not interfere with daytime activities (231). Amphetamine proved to be preferred less in the evening than in the morning, but the diazepam preferences were much the same as described above for anxious subjects. In addition, a group of older subjects (40 to 55 yr of age) was tested together with a younger group (21 to 35 yr). Neither group preferred 10 mg of diazepam to vehicle, but indeed preferred placebo to diazepam. Sedative effects did not appear to vary with age or time of day. Thus, neither anxious subjects nor normal subjects of different ages receiving diazepam at different times of day showed preference for diazepam at the doses tested.

In contrast, two sets of studies have demonstrated that insomniac patients clearly "prefer" benzodiazepines to placebo when offered for nighttime sedation. Jick et al. (532) reported that 15 mg of flurazepam clearly induced a preference over placebo in 10 of 14 insomniac subjects. This result was directly replicated in a second experiment, in which 16 of 27 subjects preferred flurazepam. However, when 15 mg of flurazepam were compared with 100 mg of secobarbital, no preference was shown for the benzodiazepine.

In another series of studies of insomniac patients, as reported by Fabre et al. (282), 0.5 mg of triazolam were preferred over placebo, over 30 mg of flurazepam, and over 500 mg of chloral hydrate. In a further comparison, 0.25 mg of triazolam were slightly preferred over 15 mg of flurazepam.

These studies of insomniacs differ in some important methodological aspects from the preference studies described previously. (*a*) These studies involved a verbal report of "preference" on a single occasion, rather than a direct measure of drug-taking behavior on repeated occasions. (*b*) The question of preference was couched in the context of usefulness as a sleep aid, and the reported amount of "preference" might have been different if the question had been presented differently.

2. Studies in psychiatric patients. The studies described below pertain to clinical use of benzodiazepines in treatment of psychiatric patients. Although these studies did not employ formal experimental techniques for assessment of abuse liability, they complement the findings of the other studies described in this section. They are considered here with respect to this context alone, and not with respect to the question of the clinical appropriateness of the psychopharmacological practices described.

Winstead et al. (1159) assessed a number of parameters of interest regarding diazepam requests in a general psychiatric ward setting. The study was carried out in a 16-bed ward over the course of 6 mo. Patients diagnosed as suffering from psychosis, neurosis, or character disorder completed an anxiety inventory upon admittance; other medications were prescribed as needed, but 10 mg of diazepam could be requested from staff at any time. There was, over this period, a positive relation between anxiety and drug-seeking behavior; the requests for the drug on average were less than one request per 2 days and declined across the 6-mo period to one request per 4 days. Unfortunately, this study did not report data by individual subjects, nor were data presented in a manner in which trends in individuals' behavior over the course of the study could be examined. These data nevertheless support the view that diazepam use does not increase over time in anxious patients.

In an outpatient study (37), 54 patients with neurotic disorders were studied over a 6-mo period. The patients were instructed to use up to six tablets of 5 mg of diazepam or placebo daily. Boxes of tablets were issued or replenished as needed. No method of confirmation of

drug ingestion was mentioned. Over the course of the 6-mo study, there was a reduction in the frequency of both diazepam and placebo use; the placebo use declined more rapidly. Over the period of the study, an average of slightly more than 5 mg of diazepam and of slightly less than one placebo tablet was consumed daily. High diazepam intake was related to severe anxiety symptomatology (as in the study described above); subjects who took more placebo were not severely anxious.

Finally, a study (499) of hypnotics and minor tranquilizers compared use following discharge to inpatient use of the same class of agent. The patients studied were 109 admissions over a 5-mo period in 1972. Diagnoses were major psychoses, affective disorders, alcoholism, and character disorders. Pharmacy records were surveyed for an average of over 8 mo following discharge; records were confirmed by contacting slightly less than half of the patients for whom the records were totally accurate. Ten patients had received prescriptions for hypnotics, chiefly flurazepam or chloral hydrate. Those that were prescribed flurazepam continued to take it on an outpatient basis; this was not the case with chloral hydrate. No quantitative measurements of use were provided for the outpatient portion of the observation, rendering the data virtually uninterpretable.

In short, these studies suggest that, when available upon demand, diazepam is self-administered at a low frequency. Additionally, there seems to be an association between severity of anxiety and amount of drug used. This finding appears at variance with the results reported by de Wit et al. (229), which indicated that, in more formal experimental conditions, using subjects with high anxiety scores but not clinically anxious patients, there was no relationship between level of anxiety and preference for diazepam. Finally, when benzodiazepine use is patient regulated in these psychiatric settings, it tends to decline over time.

3. Studies in subjects with histories of sedative or alcohol abuse. a. STUDIES COMPARING BENZODIAZEPINES AND NONBENZODIAZEPINES. **i. Studies of reinforcing effects.** A series of interesting studies by Griffiths and his colleagues has compared pentobarbital to diazepam. In one study (393), subjects were males with documented histories of abuse of sedatives and other drugs. An initial trial day was designed to afford familiarity with the effects of a drug later to be tested as a reinforcer; during this day, each subject was given the opportunity of requesting up to ten doses of the drug assigned to him, at intervals of at least 15 min between ingestions. Over a succeeding 10-day period, subjects were required to ride a stationary bicycle for 15 min in order to receive each drug ingestion. Chlorpromazine (25 or 50 mg), pentobarbital (30 or 90 mg), and diazepam (10 or 20 mg) were compared with respect to the amount of self-administration behavior maintained. Neither dose of chlorpromazine was distinguished from placebo. Pentobarbital at 90 mg/ingestion maintained relatively stable self-administration responding, i.e., between six and nine ingestions per day; the smaller dose (30 mg/ingestion) maintained two to four ingestions per day toward the end of the 10-day period. Diazepam self-administration never achieved a stable rate and was declining throughout the 10-day period, with response to the higher dose (20 mg) declining more slowly than response to the lower dose (10 mg). Exposure to the intermediate dose of pentobarbital, and to both doses of diazepam, was associated with considerable interindividual variation in amount of self-administration behavior across the 10-day period. The subjective effect questionnaire showed significant self- and staff-rated intoxication with each drug tested; effects produced by the two chlorpromazine doses were similar, whereas there was a clear dose-related increase in ratings of intoxication for both pentobarbital and diazepam. The intensity of subjective effects as rated by subjects showed similar effects for the higher doses of pentobarbital and diazepam, but pentobarbital (90 mg) produced more consistent self-administration than diazepam (20 mg). Thus, this study established one method in which the drug self-administration procedures used in animals could effectively be extended to studies in sedative abusers. It also showed that, at the doses studied, diazepam produced a slight increase in self-administration, though the stability of self-administration over time was questionable.

In an earlier study from the same laboratory (392), when the response cost (time required to ride the bicycle) for each ingestion was varied, self-administration of both pentobarbital (30 mg) and diazepam (10 mg) was reduced at higher response requirements. The majority of response costs were below those required in the experiment described above (393), and in these lower-cost conditions, both drugs maintained self-administration more effectively than in the above experiment.

In a study of dose and drug preference (395), a variety of doses of diazepam (50 to 400 mg) and pentobarbital (200 to 900 mg) were evaluated relative to placebo. Increasing doses of pentobarbital led to increases in subjective reports of drug effect and to increases in preference. The diazepam dose comparisons (50 versus 100, 100 versus 200, 100 versus 300, and 100 versus 400 mg) produced minimal subjective effects and no marked preference for the higher dose. When pentobarbital (400 mg) and diazepam (200 mg) were compared under conditions in which they produced comparable subjective and staff ratings of drug liking and effect, each subject indicated preference for pentobarbital. The high doses of diazepam employed in these studies produced changes in subjects' mood and behavior, e.g., increased complaining, dysphoria, and disruptiveness. The high doses of diazepam were preferred over placebo, even when these doses had little subjective effect.

Thus, diazepam has not been identified as a compound that will produce a reinforcing effect at doses in the therapeutic range in normal or anxious subjects. In sedative abusers, however, larger doses of diazepam (20 to 200 mg) may be reinforcing. This disparity in findings of studies of normal subjects and sedative abusers may

prove to be due to one or more of a number of procedural differences in the conduct of the studies reported, as well as to difference in the doses tested.

In this connection, a study of Healey and Pickens (446) is of interest. These investigators studied ten subjects with histories of significant sedative abuse. In two series of observations, they examined preference between alternative doses of diazepam at 2, 5, 10, 20, and 40 mg, i.e., doses covering the range generally recommended for therapeutic use; and preference between pentobarbital at 30 or 50 mg and this same range of diazepam doses. Subjects showed no preferences among the various doses of diazepam. Two of six subjects preferred 20 mg of diazepam over 30 mg of pentobarbital; no clear preference was shown between any dose of diazepam and 50 mg of pentobarbital. In this study, subjects were given the opportunity to self-administer drug doses at intervals of no less than 30 min. They were informed that this opportunity would be curtailed if they became excessively intoxicated; this seldom occurred.

Taken in conjunction with the preference studies of normal and anxious subjects (536, 229), the study of Healey and Pickens suggests that the preference for diazepam exhibited in the studies reported by Griffiths and his coworkers may be attributable to the high doses they employed.

Bechelli et al. (58) compared the effects of single doses of triazolam (0.25 mg) and zopiclone (3.75 mg) in subjects undergoing detoxification from alcohol. The test drugs were provided in capsules of two different colors; each drug was provided in capsules of each color. After initial forced-choice exposures to each drug, subjects were given a choice between the two on the fifth and sixth day of withdrawal. Fifteen subjects chose zopiclone and 25 chose triazolam; this difference was statistically significant. The subjects reported that both drugs were similar to alcohol with respect to subjective effects. There were no marked changes in ratings on the POMS nor significant changes in ARCI subscale measures. Both drugs produced increased reports of side effects, e.g., sleepiness. The authors concluded that triazolam was preferred to zopiclone. The significance of these findings is unclear because only single doses of the drugs were tested.

A similar protocol was used to compare the same doses of triazolam and zopiclone in a study reported by Boissl et al. (109). In this study, subjects going through alcohol withdrawal were permitted to self-administer up to eight capsules per day (for a maximum of 2 mg of triazolam or 30 mg of zopiclone). The 40 subjects were told that the experiment was investigating the ability of the two drugs to replace alcohol. After 24 h free of psychoactive drugs, the subjects were given eight capsules (color-coded as in the study described above) of one drug daily for 2 days, and they were then crossed over to the same schedule for the other drug. They were told to take a capsule every time they felt like taking a drink of alcohol. The study examined symptoms of intoxication, mood as rated on the POMS scale, a side-effect checklist, ARCI ratings, and a preference questionnaire. On the fifth and sixth days, subjects were given a choice between the two drugs. Twenty-two subjects expressed a preference for triazolam, and 18 for zopiclone; this difference was not significant. Triazolam produced a slightly higher score on the ARCI drunkenness subscale and the PCAG (phenobarbital-chlorpromazine-alcohol group) subscale. There were some minor differences in effects as rated on the POMS scale. Thus the results of this study differed from those reported by Bechelli et al. (58), despite the fact that the studies examined the same doses and used closely similar protocols.

Although this was not a study of sedative abusers, we mention here a study by Preston et al. (887, 886), who examined self-administration of oxazepam (30 mg/day), clonidine (0.3 mg/day), and hydromorphone (3 mg/day) in subjects undergoing methadone detoxification. Oxazepam did not support preference nor maintain self-administration, although hydromorphone did. The significance of these findings is unclear because only single doses of each drug were tested.

ii. Studies of subjective effects. Roache and Griffiths (925) compared triazolam (0.5 to 3 mg) and pentobarbital (100 to 600 mg) with respect to effects on psychomotor performance and reports of subjective drug liking in two groups of subjects with histories of drug abuse. The highest dose of pentobarbital produced greater liking scores than the highest dose of triazolam. On the other hand, triazolam produced greater performance deficits than pentobarbital. It is not clear that these differences were found using appropriate dose comparisons; higher doses of triazolam might have achieved plateaus in drug-liking scores equivalent to those observed with pentobarbital.

It might further be noted that this study (925) exemplifies the kind of experiment that appears to be becoming a standard in abuse liability assessment, in that a variety of measures of performance effects and of drug liking are employed in the same protocol. Although the study examines drug liking, it does not measure reinforcing effects of the drugs studied. In our view, since it has not yet been established that these effects always covary, experiments should continue to assess reinforcing effects directly.

Another study by Griffiths et al. (394) compared the effects of high doses of diazepam and of pentobarbital on a variety of psychomotor tasks, subjective ratings, and measures of sociability. The subjects were 12 males with histories of abusing both barbiturates and benzodiazepines for over a decade; they reported preferences for either diazepam or barbiturates as their favorite sedatives (although preference was not directly measured in this study). Three of the subjects were in regular methadone maintenance treatment and continued this treatment during the experiment. A single dose of diazepam (50 or 100 mg), pentobarbital (200 or 400 mg), or placebo was administered each day for 5 consecutive days. Each dose of diazepam and of pentobarbital pro-

duced dose-related effects on psychomotor tasks, daytime sleeping, and ratings of the magnitude of drug effects. Diazepam, but not pentobarbital, produced a dose-related decrement in positive mood and in staff-rated measures of sociability, as well as increases in hostility; these effects were most evident on the third through the fifth days of treatment.

Cole et al. (185) compared subjective effects of 10 and 40 mg of buspirone, 300 mg of methaqualone, 10 and 20 mg of diazepam, and placebo in college students who reported recreational use of sedative-hypnotics. Subjective effects were measured on Addiction Research Center Inventory (ARCI) scales. All groups received all treatments, which were spaced at weekly intervals. Methaqualone produced increases in ratings on the morphine-benzedrine group (MBG) and PCAG subscales. Buspirone caused increases in ratings of sedation and dysphoria. Twenty mg of diazepam elicited higher euphoria ratings than 10 mg after 1 h. These were significantly higher than those associated with 10 or 40 mg of buspirone. The subjects could discriminate 40 mg buspirone from placebo, though this was not associated with ratings of euphoria; buspirone was more sedating than placebo but not as sedating as methaqualone. On a novel scale, which the investigators derived from the ARCI, 40 mg of buspirone were associated with fewer desirable subjective effects than methaqualone, diazepam, or the smaller dose of buspirone.

Another evaluation of buspirone was reported by Griffith et al. (388), who compared three doses (10, 20, and 40 mg) of buspirone and two doses (10 and 20 mg) of diazepam in 19 male volunteers who had been hospitalized for treatment of alcohol dependence. Each dose of each drug was given to each subject at 3-day intervals. Neither drug had significant effects on blood pressure, pulse, respiration, or body temperature, though the higher doses of buspirone produced transient pupillary constriction. Diazepam produced modest effects on ARCI ratings, similar to those reported in other studies. There were also mild sedative effects associated with the highest dose of buspirone. The investigators noted that buspirone was generally less well liked than diazepam, though the questionnaire data relevant to liking medication do not appear to support this suggestion. The authors also concluded that buspirone at high doses may produce dysphoria, as previously reported by Cole et al. (185), but the basis for this claim in the data reported is not very clear.

b. STUDIES COMPARING DIFFERENT BENZODIAZEPINES.

i. Study of reinforcing effects. Griffiths et al. (399) compared preferences of sedative abusers for diazepam, oxazepam, and placebo. The dose of diazepam was varied over a 4-fold range and compared to a high dose of oxazepam. At the lowest dose of diazepam (40 mg), oxazepam (480 mg) was chosen on 62.5% of the opportunities. As the diazepam dose was increased, the proportion of choices of diazepam increased. At the highest dose (160 mg), diazepam was chosen on 91.7% of the opportunities. Diazepam was approximately 8 times more potent than oxazepam under this procedure. Upon interview, subjects indicated that the relatively fast onset of action led to the choice of diazepam over oxazepam.

ii. Studies of subjective effects. Griffiths et al. also reported (398) another study of a variety of doses of diazepam and oxazepam in sedative abusers. Drug effects were assessed using standard measures of performance on psychomotor tasks and staff ratings of euphoria, daytime sleepiness, etc. Single doses of the test drugs (diazepam, 10, 20, 40, 80, 160 mg; oxazepam, 30, 60, 120, 240, 360, 480 mg) were given only every third day under double-blind, counterbalanced conditions. Subjects were studied under one drug condition and then changed to the other; doses were studied in ascending sequence. Diazepam was more potent in producing liking scores, as well as in producing psychomotor and cognitive effects. The onset of its effect and time to peak effect were more rapid than those of oxazepam. The drugs exhibited similar effects with respect to psychomotor decrements and drug-liking scores. With regard to some measures of psychomotor performance or subjective effects, oxazepam appeared roughly one-third to one-fifth as potent as diazepam. At the highest doses, maximal effects on liking were somewhat less for oxazepam than for diazepam, although complete dose-effect curves were not obtained. This study was more effective than previous studies in showing dose-dependent effects of diazepam in this subject population, possibly because it used longer intervals between administration of test doses. There was a suggestion that tolerance developed to a number of effects of oxazepam, while such tolerance was not seen with diazepam.

In experimental circumstances where diazepam and triazolam produced comparable subjective effects and performance decrements in subjects with histories of sedative abuse, Roache and Griffiths (926) also found tolerance development with diazepam but not triazolam. The conditions for such tolerance development have not been studied in detail.

Funderburke et al. (325) compared the effects of 10 to 40 mg of diazepam and 1.5 to 6 mg of lorazepam in two groups of recreational benzodiazepine users. Each dose of each drug was administered for 4 consecutive days, with 1-wk intervals between dosing sessions. A series of psychomotor performance and memory measures was taken, as well as subjective drug-liking measures. The highest dose of lorazepam produced more prolonged effects on all measures than the highest dose of diazepam.

Orzack et al. (831) compared the subjective effects of single doses of diazepam (10 mg), prazepam (20 mg), and placebo in young outpatients who were recreational sedative users. These subjects failed to identify reliably the drug conditions from placebo, nor did they rate either of the drug conditions as different from placebo on a drug intoxication ("high") measure. The ARCI measures of drunkenness, sedation, and PCAG scores were elevated by both prazepam and diazepam.

Using measures derived from the ARCI, Jaffe et al. (520) reported that halazepam (160 mg, 320 mg) had a slower onset of subjective effects than diazepam (20 mg, 40 mg) in male patients recently treated for alcohol withdrawal. There was a tendency for halazepam to produce less intense subjective effects than diazepam at the time of apparent peak effects.

c. STUDIES COMPARING SUBJECTIVE EFFECTS OF DIFFERENT BENZODIAZEPINES AND NONBENZODIAZEPINES. Two reports compared the subjective effects of chlordiazepoxide and diazepam with those of pentobarbital, as assessed by volunteer inpatient alcohol and sedative abusers (524, 523). Oral doses of diazepam (10, 20, and 40 mg) and of chlordiazepoxide (100, 200, and 400 mg) produced, in a dose-dependent manner, subjective effects similar to those of pentobarbital (120 to 240 mg); diazepam was 10 times more potent than pentobarbital, and chlordiazepoxide was half as potent as pentobarbital. The time courses of the drugs' subjective effects were similar.

Cole et al. (186) studied the effects of 20 mg of prazepam, 10 mg of diazepam, 200 or 400 mg of methaqualone, and placebo in male and female subjects who were recreational users of sedative-hypnotics; the drug doses were selected to represent high standard therapeutic doses. Each subject served as his own control. Subjects were instructed not to drink alcohol for 12 h before each testing session, and not to take any drugs for 72 h preceding tests. Methaqualone produced significant effects on the MBG and PCAG scales of the ARCI; the two doses of methaqualone were essentially identical, with peak effects appearing in 1 h. Effects on these scales produced by diazepam and prazepam were less than those produced by methaqualone. Neither diazepam nor prazepam produced effects on these scales that were statistically significantly different from those produced by placebo.

4. Studies of alcoholics in outpatient treatment. Since the population of alcohol abusers should be considered to be at increased risk of other forms of drug abuse, there is reason to be concerned about their developing psychological dependence on the benzodiazepines that have been prescribed as adjuncts in the treatment of alcoholism. Kryspin-Exner and Demel (614) treated 491 alcohol-dependent patients with anxiolytic agents and observed the number who increased their dose of medication. The average period of treatment was 1 yr; the minimum was 4 wk. Of 111 patients treated with chlordiazepoxide, 4 (3.6%) showed a tendency to increase their dose; of 302 patients treated with diazepam, 7 (2.3%) tended to increase their dose; and of 78 patients treated with meprobamate, 6 (7.6%) tended to increase their dose. Of the 11 patients who increased their doses of the benzodiazepines, 7 had abused sedatives or analgesics in addition to alcohol.

This observation indicates a low rate of abuse of benzodiazepines in recovering alcoholics. This is supported by a second study, described in the same report (614), in which hospitalized, recovering alcoholics were given access to either placebo, in one group, or diazepam, in another group. Patients could take up to ten tablets per day; diazepam was supplied in 5-mg tablets. Both groups were instructed to use their medication as needed for self-treatment of "withdrawal symptoms." Over a period of 32 days, there was no greater ingestion of diazepam than of placebo. In a separate study, subjects who had been abusing hypnotics or drug combinations showed a stronger tendency, over the course of several weeks, toward increasing their doses of benzodiazepines (oxazepam, lorazepam, diazepam, and nitrazepam), although this tendency among subjects given access to benzodiazepines was less pronounced than in subjects given access to meprobamate or clomethiazole.

This series of studies suggests that former abusers of hypnotics and drug combinations are more likely to self-administer higher doses of benzodiazepines than are recovering alcoholics. The latter group shows very little tendency to escalate their dose over the recommended therapeutic level. A similar finding was reported by Rothstein et al. (943), who prescribed chlordiazepoxide or diazepam for outpatients recovering from alcohol dependence, with instructions to take the medication as needed for relief of anxiety or tension. Of 108 patients followed for at least 1 yr, 86% reported that they did not take the medication on a daily basis, and 50% discontinued use for at least 30 days during the study period. Some evidence of abuse or misuse was noted in 5% of the patients, including instances of self-treatment for alcohol withdrawal symptoms as well as instances of increasing chlordiazepoxide consumption.

5. Summary and discussion. It seems clear that, apart from subjects with histories of drug abuse, the benzodiazepines have little or no reinforcing or preference-inducing effects. No study in normal subjects has shown a striking preference for any of the benzodiazepines over placebo; this applies as well to studies of anxious subjects, for whom these medications are most frequently prescribed. These findings would suggest that it is unlikely that use of these drugs in these patient populations is associated with a significant risk of abuse. It should be noted, however, that to date the protocols used for studies in these subjects have not detected the reinforcing effects of sedative drugs with demonstrated abuse liability; for example, while they have readily shown the reinforcing effects of amphetamine, they have not yet demonstrated preference for pentobarbital. Also, these protocols have yet to be used to study other benzodiazepines, such as triazolam or midazolam, drugs which—to judge from their reinforcing effects in animals—might be more likely to induce a preference in humans.

Nevertheless, in subjects who have histories of abuse of sedatives, including abuse of benzodiazepines, it is possible to demonstrate a preference for benzodiazepines over saline or vehicle. A number of studies have, however,

shown that short- or intermediate-acting barbiturates (e.g., pentobarbital) have a greater capacity to induce preference or to produce subjective effects than any of the benzodiazepines studied to date.

Some investigators have shown a tendency to relinquish studies of drug preference in favor of measures that are less directly related to reinforcing properties, e.g., subjective effects such as drug liking. Until it has been established that such subjective effects consistently covary with measures of reinforcing effects, such as preference, reinforcing effects should continue to be measured directly.

Some studies have found differences between individual benzodiazepines with respect to subjective effects or to preference for one compound over another. Such findings to date are limited to individual experiments; however, they are of sufficient interest that they merit further study. Likewise, some experiments have indicated potential differences between benzodiazepines with respect to subjective effects and concomitantly measured effects on psychomotor performance. These findings also remain for the large part single-experiment results; should these effects continue to be demonstrated, they too would assume greater significance for assessment of the abuse liability of the class and of the relative abuse liability of the individual agents.

Clearly the future of this area of research lies in evaluation of the validity of the experimental measures that have been applied to assessment of the benzodiazepines' liability for abuse, i.e., in the relation of these laboratory measures to various epidemiological measures of the abuse of these drugs attendant on their extensive medical use.

D. Summary and Discussion

Experimental investigation of drug self-administration is one of the most interesting areas in behavioral pharmacology, in part because it tests the validity of behavioral approaches to abuse liability assessment. It also provides an important basis for determining parallels between animal and human research in this area.

Assessment of abuse liability can be approached using a variety of human populations. A number of experiments have studied self-administration and related measures in subjects with histories of sedative abuse. At the other extreme are subject populations who have had little or no exposure to psychoactive drugs, and who are not affected by the conditions for which such drugs are medically indicated. This contrast serves as an interesting fulcrum for comparison of the available evidence regarding the reinforcing effects of the benzodiazepines.

In animals, intermediate-acting barbiturates maintain self-administration behavior more effectively than do benzodiazepines; this differentiation has been shown under a variety of experimental conditions. Studies in sedative abusers have demonstrated a corresponding difference in the reinforcing effects of pentobarbital and diazepam; this difference appears across different measures in these human subjects as well, including measures of drug preference and of operant behavior maintained by drug administration.

These parallel findings in animals and humans hold promise for the expansion of these techniques in research on other substances. They suggest that other drugs that serve as reinforcers in animals might be expected to serve as reinforcers in sedative abusers as well. For example, among the benzodiazepines, based on the evidence of their effects in animals, it might be expected that triazolam and midazolam would show reinforcing effects in sedative abusers; it should be noted, however, that human studies have found that triazolam is not similar to pentobarbital with respect to subjective effects.

As these findings suggest, there may be differences between measures of reinforcing and subjective effects in humans. Experimentation in human self-administration is an immature and developing branch of research. It would be incautious to suppose, on the basis of early studies, that one measure might have precedence over another. We would therefore advocate that investigators continue to measure reinforcing effects, drug preference, and subjective effects.

While studies in sedative abusers have yielded interesting information, drugs may have strikingly different effects in other subject populations. For example, it has yet to be demonstrated that any benzodiazepine, or for that matter any other sedative agent, has significant reinforcing effects or induces preference in subjects who do not have histories of sedative abuse.

III. Studies of Physiological Dependence

A. Introduction

"Physiological dependence" is synonymous with "physical dependence," but the former term is used here because it more clearly reflects the types of observations made in determining that dependence has developed. As used in this review, *physiological dependence* indicates a state of an organism during drug treatment such that discontinuation of this treatment is followed by the development of a time-limited withdrawal reaction that can be reversed by resumption of treatment. (This definition unavoidably poses some problems in research as well as clinical settings, since it indicates that physiological dependence to a particular drug regimen can be determined only after the regimen has been discontinued.) It is important that this definition characterizes the withdrawal syndrome as time limited. In treatment of a disorder by chronic drug administration, discontinuation of medication may lead to the reappearance of those symptoms that originally indicated the need for treatment; since these symptoms can persist indefinitely following the termination of drug treatment, they should not be construed as part of the withdrawal syndrome.

Most of what we know about the development of

dependence in general has come from extensive studies in laboratory animals and clinical studies in humans of opioid, barbiturate, and ethanol administration and withdrawal. From these studies the following general points can be made: (*a*) each pharmacological class of drugs has its own characteristic set of withdrawal signs; (*b*) the higher the dose and the longer the duration of treatment, the more severe the withdrawal reaction (up to some maximum); and (*c*) the withdrawal signs can usually be rapidly and completely reversed by the administration of the drug that produced the dependence and by other drugs in that class; while drugs of other pharmacological classes may attenuate some of the individual signs of withdrawal, they will not reverse the entire syndrome.

An implication of the second point is that the development of dependence will depend in part on the pharmacokinetics of the compound. Thus, a short-acting drug must be given frequently to produce dependence, while a long-acting drug can produce dependence if given less frequently. The duration of action of a drug also partly determines the time course of the observed withdrawal signs. Other things being equal, the more quickly a drug is eliminated from the body, the more quickly the withdrawal signs will develop and the more severe they will be. A drug that is eliminated relatively slowly will result in a less intense withdrawal reaction, since the slow elimination produces a gradual tapering of drug effect. The administration of a drug antagonist, which temporarily removes the dependence-producing drug from its sites of action, can produce immediate and severe withdrawal signs. This has been well described in the case of narcotic antagonists and, with the development of benzodiazepine antagonists, researchers have gained an important tool in the study of precipitated withdrawal from these drugs as well.

Withdrawal signs have been used as one method of drug classification. Thus, drugs that reverse morphine dependence are considered as members of a particular opioid class, and drugs that reverse ethanol dependence are included in a separate sedative-hypnotic class. A drug that reverses the signs of withdrawal from another drug is likely to produce a similar type of dependence. Benzodiazepines are quite effective in reversing withdrawal from ethanol and barbiturates and could thus be expected to produce a withdrawal reaction similar to these sedative-hypnotics.

The withdrawal signs that develop following drug discontinuation are frequently opposite to the direct effects of the drug itself. Thus, morphine produces pupillary constriction on acute administration in humans, and one sign of morphine withdrawal is marked pupillary dilation. These "rebound" withdrawal effects have contributed to some fundamental theories of the basis of drug tolerance and dependence on a molecular level (368); neuronal rebound phenomena have been reported in the spinal reflex system of rats during withdrawal from chlordiazepoxide (950). Despite the customary inclusion of rebound effects among phenomena considered to represent signs of withdrawal from narcotics and sedatives, some investigators have chosen to exclude such effects from their consideration of benzodiazepine withdrawal phenomena; as discussed later in this section, this position is arbitrary and inappropriate.

Previous reviews to which the reader might wish to refer include general reviews of physiological dependence on drugs acting on the CNS (515, 1141), a review of physiological dependence specifically on benzodiazepines (633), and a recent conceptual review of dependence on benzodiazepines (415) that provides a good treatment of rebound phenomena.

B. Studies in Animals

Animal studies of physiological dependence on benzodiazepines have been of two types. One involves the study of cross-dependence. Dependence is produced to a prototype compound (usually a barbiturate) with known withdrawal characteristics, and the capacity of the test benzodiazepines to prevent or reverse withdrawal from the prototype is examined. The second type examines the capacity of a benzodiazepine to produce a state of physiological dependence directly, as a consequence of its chronic administration. The recent availability of benzodiazepine-receptor antagonists has provided the opportunity to measure precipitated withdrawal reactions. This has led to several interesting parametric studies of the development of physiological dependence to benzodiazepines.

Previous publications pertinent to this research, to which readers might wish to refer, include a general treatment of abuse liability assessment (1085) and more recent reviews by Yanagita (1178), Martin (719), and Rosenberg and Chiu (932), which focus more specifically on assessment of benzodiazepines.

1. Cross-dependence studies. Cross-dependence studies assume that a drug that completely reverses the withdrawal signs of a prototype compound will produce a similar type of dependence if the drug itself is repeatedly administered in appropriate doses and frequencies. Although this assumption appears to be valid with respect to some pharmacological classes of drugs (992), and although this is an economical procedure for evaluating a series of compounds, the validity of the assumption with respect to drugs prescribed for sedative or hypnotic effects has not been rigorously tested. In fact, there is some indication that some drugs that suppress barbital withdrawal do not produce a similar type of physiological dependence. Carisoprodol, a propanediol, prevented barbital withdrawal in dogs (221) but did not appear to produce significant dependence itself (315, 314). In contrast, meprobamate, which is chemically similar to carisoprodol, both suppressed barbital withdrawal and produced physiological dependence (1195). These results emphasize that all drugs that substitute for a prototype

compound may not produce the same degree or type of dependence as the prototpye.

Most cross-dependence studies of benzodiazepines in rodents have rendered rats or mice dependent on either barbital or phenobarbital and studied effects of chlordiazepoxide or diazepam, typically on one withdrawal sign (e.g., refs. 59 and 817). Although important details (e.g., route of administration) were missing in many of the reports, they indicated that various withdrawal signs, such as sound-induced convulsions, irritability, muscle rigidity, tremor, weight loss, and decreased eating, were reversed by diazepam (59, 567, 801, 912, 1071, 1090, 1204), chlordiazepoxide (567, 813, 817, 1090), nitrazepam (567, 1071, 1070), and prazepam (801). Recently, Tagashira et al. (1073) reported that nitrazepam, added to food, produced a more complete attenuation of phenobarbital withdrawal than did diazepam (20 to 40 mg), which failed to suppress tremor and anorexia. In dogs, convulsions and "delirium" produced by barbital withdrawal were also reversed by chlordiazepoxide (221, 813).

Using rhesus monkeys in a manner similar to their use in assessing opioid cross-dependence (cf. 992), Yanagita and Takahashi (1195) reported that diazepam, chlordiazepoxide, and oxazolam suppressed signs of barbital withdrawal. That the suppression of withdrawal was not due to a nonspecific sedative effect was suggested by results with other drugs that are neither benzodiazepines, propanediols, nor barbiturates. Two tricyclic compounds, perlapine and benzoctamine, produced sedation in normal monkeys but did not suppress barbital withdrawal signs.

Yanagita and colleagues subsequently conducted a series of experiments on cross-dependence between benzodiazepines and barbital, and some of these studies have been reviewed (1178). These studies have shown that many of the benzodiazepines examined, as well as the nonbenzodiazepine zopiclone, suppressed barbital withdrawal to a similar extent and differed only in potency. A few drugs suppressed only some of the signs of withdrawal, or did not completely suppress all signs of withdrawal, at the highest doses studied (see table 1). These findings taken together thus suggest some differences among benzodiazepines with respect to their efficacy in suppressing signs of barbital withdrawal.

Similarly, Stockhaus (1049) found that, relative to therapeutic doses, higher doses of brotizolam than of three other benzodiazepines were required to suppress barbital withdrawal in rhesus monkeys; nitrazepam was more potent than diazepam, which was in turn more potent than triazolam (see also ref. 615).

There is generally a high concordance between the potency of those benzodiazepines that suppress barbiturate withdrawal (1178) and their K_i values for displacement of [^{3}H]diazepam (778), among the drugs that have been studied under both procedures (refer to table 1). These results indicate that activity at the benzodiazepine receptor may be closely related to the suppression of barbital withdrawal. This was supported by studies of Wakasa et al. (1124), who demonstrated that 4 mg/kg of diazepam attenuated barbital withdrawal, but that the withdrawal signs returned following administration of the benzodiazepine-receptor antagonist flumazenil (Ro 15-1788); flumazenil did not reverse the capacity of pentobarbital to attenuate diazepam withdrawal, although pentobarbital did attenuate some signs precipitated by flumazenil in diazepam-dependent monkeys.

Diazepam reversed ethanol withdrawal in rhesus monkeys (776) and mice (92, 1177), suggesting that benzodiazepine cross-dependence with ethanol was similar to that shown with barbital and phenobarbital. This cross-dependence likely underlies the utility of benzodiazepine therapy in ethanol withdrawal (549).

It is of interest to compare the degree of dependence produced by benzodiazepines with that produced by bar-

TABLE 1

Minimal doses that suppressed barbital withdrawal in rhesus monkeys discontinued from 150 mg/kg/day for 28–30 h (based on studies by Yanagita and colleagues)

Study	Drug	Dose (mg)	K_i values*
	Drugs producing complete suppression		
1190	Clonazepam	0.25, 1.0	1.5
1186	Fludiazepam	1.0	
1189	Flutoprazepam	1.0	
1200	Estazolam	2.0	
1193	Haloxazolazepam	2.0	
1196	Prazepam	4.0	
1191, 1195	Diazepam	5.0	6.3
1185, 1179	Diazepam	8.0	6.3
1185, 1179	Zopiclone	8.0	
1180	Mexazolam	10.0	
1188	Clorazepate	16.0	41.0
1169	Cloxazolazepam	20.0	
1173	Chlordiazepoxide	20.0, 40.0	220.0
1173	Oxazolam	20.0, 40.0	
	Drugs producing incomplete suppression		
1187	Triazolam	1.0	
1184	Flunitrazepam	1.0	2.8
1201	Alprazolam	2.0	
1181, 1183	Nitrazepam	2.0, 4.0	6.4
1182	Ethyl loflazepate	4.0	
1198, 1183	Lorazepam	10.0, 12.0	2.7
1181	Quazepam	16.0	
1202	Clobazam	3.0	
1183	Lormetazepam	256.0	
1181, 1192	Halazepam	320.0	

* Mohler and Okada (778); K_i values determined from 50% inhibitory concentration values for displacement of specific [^{3}H]diazepam binding to crude synaptosomal preparations from rat cerebral cortex. Specific binding was defined as the difference between total binding (binding in the absence of 1 μM diazepam) and nonspecific binding (binding in the presence of 1 μM diazepam). Nonspecific binding was at most 5% of total binding.

biturates, since there is considerable cross-dependence between these two classes of drugs. Boisse et al. (108; see also refs. 949 and 343) used the "chronically equivalent" dosing technique to compare the dependence-producing effect of chlordiazepoxide with that of phenobarbital. In many respects, signs of withdrawal were similar for the two drugs and included piloerection, tremor, twitching, hypertonia, and weight loss. Convulsions occurred only with phenobarbital. Additionally, several graded signs appeared to be significantly less intense for chlordiazepoxide than for phenobarbital. Martin et al. (718) noted some differences in withdrawal signs seen after repeated administration of diazepam or pentobarbital. The signs that were specific for the different agonists were, for pentobarbital, seizures and grand mal convulsions, and for diazepam "explosive awakening" (a rigid jump or turn which propelled the rat against the sides or top of the cage). Martin et al. concluded that the withdrawal syndromes produced by the two drugs were qualitatively different and not due to the differences in the pharmacokinetics of the drugs. The most compelling argument for the qualitative nature of the differences was that, while each drug partly suppressed the withdrawal syndrome of the other, the effects were not dose dependent, and there appeared to be a plateau in the dose-effect curves. For example, pentobarbital withdrawal was suppressed in a dose-related manner by pentobarbital. In contrast, diazepam produced maximal suppression of pentobarbital withdrawal signs at a dose of 10 mg/kg; a 4-fold increase in diazepam dose did not produce a greater suppression of pentobarbital withdrawal.

The results of Martin et al. (718), showing incomplete cross-substitutability of diazepam and pentobarbital, are in contrast to earlier cross-dependence studies in rodents and in primates (e.g., 1178), which showed that several benzodiazepines completely suppressed barbital withdrawal. An important difference between some of those studies and the one by Martin et al. may be the degree to which the investigators attended to individual signs of withdrawal. Martin et al. presented some information on a variety of withdrawal signs and how those signs contributed to the withdrawal score. Most investigators did not present quantitative information or examined only a single sign.

2. Primary dependence studies. a. WITHDRAWAL INDUCED BY DRUG DISCONTINUATION. Primary dependence studies on the surface appear more straightforward than cross-dependence studies. In these studies, a drug is administered repeatedly for some period of time, and withdrawal signs are recorded when drug administration is discontinued. Since dependence is presumably more likely to develop, or to be of greater magnitude, with greater exposure to drug, attempts often are made to administer the highest tolerable dose of the drug. In some studies, initial doses of the agonist were increased as tolerance developed to the sedative effects, although the doses were not always increased in a systematic manner. In other studies, a particular dose was chosen and administered without change for the duration of the drug period. Another method of studying dependence is the "chronically equivalent" dosing procedure, in which the dose is continually adjusted in order to achieve a relatively stable degree of drug effect throughout the drug-administration period (934). Utilizing this technique, drugs that differ in potency and duration of action can be directly compared by first establishing the respective doses required to produce an equal degree of effect and then adjusting the dose throughout the study period so as to maintain comparability of effect (cf. 103). Although it is labor intensive, the "chronically equivalent" dosing technique is an important method of comparing dependence-producing capacities of different drugs.

Most primary dependence studies of benzodiazepines in rodents have examined withdrawal after chronic p.o. administration of diazepam or chlordiazepoxide, although dependence to benzodiazepines has also been demonstrated when the drugs were placed in the animals' food ration (329, 1204). In some studies, doses of diazepam have been as high as 160 to 300 mg/kg/day. In the study in which doses of diazepam reached 300 mg/kg/day, convulsions were observed during withdrawal (1206). Withdrawal signs in rodents have also been observed after much lower dose regimens; Voiculescu et al. (1122) reported sound-induced seizures in 43% of rats that had received 3 mg/kg/day of diazepam for 40 days, and in 12% of mice that had received 1 to 2 mg/kg of diazepam for 6 to 20 days. Other withdrawal signs reliably observed after treatment with various doses of diazepam were weight loss, increased locomotor activity, tremor, muscle rigidity, and decreased eating (43, 117, 718, 1064, 1072, 1203–1207). Similar signs have been observed in rats withdrawn from chlordiazepoxide (108, 107, 813, 948, 949, 1203, 1206), N-desmethyldiazepam (719), oxazepam (719), and midazolam (836). Increased susceptibility of mice to pentylenetetrazol-induced seizures was noted by Gonzalez et al. (370) following daily i.p. administration of 1 mg/kg of triazolam for 14 days.

Several investigators have observed withdrawal effects after chronic administration of benzodiazepines in primates. Yanagita and colleagues (1195) found withdrawal characterized by a variety of signs (see below) following chronic administration of diazepam, oxazolam, or chlordiazepoxide. Killam et al. (579), studying baboons, noted EEG changes characterized by abnormally marked seizure responses to flashing lights and changes in the power spectrum. These effects were observed in 3 of 11 subjects following daily doses of diazepam as low as 0.4 mg/kg/day for 112 days or, in 2 of 7 subjects, following daily doses of clonazepam (Ro 5-4023) as low as 0.02 mg/kg/day for 84 days. There was no report of signs other than these EEG changes. Lukas and Griffiths (683, 684) observed overt signs of withdrawal such as nose rubbing, yawning, and tremor in baboons following 45 days of i.g. administration of 10.0 mg/kg of diazepam twice per day.

i. Effects of dose. Most studies of primary dependence in animals have examined the effects of relatively high doses. Possibly because study of even a single dose entails extensive work, very few studies have examined the effects of more than one dose on the withdrawal syndrome observed when the drug is discontinued. Using the "chronically equivalent" dosing technique, Boisse et al. (107) examined the effect of dose level, frequency, and duration of administration of chlordiazepoxide on the number and intensity of withdrawal signs. Following 35 days of repeated administration of doses that were adjusted daily to produce a specific degree of ataxia, the average final dose was 435 mg/kg. With the end of treatment, withdrawal was graded as severe, and 15 of 20 withdrawal signs were obtained per subject. In subjects treated for 35 days with doses that produced anesthesia, the final dose was 975 mg/kg. The withdrawal was also graded as severe in these subjects, and the average number of withdrawal signs was 14.5. Thus, at these dose levels for this duration of treatment, there was little difference in effect of dose over a 2-fold range of doses.

In a later study, Guarino et al. (408) found the graded severity of withdrawal to be related to dose over a lower range of doses. In this study, fixed doses of chlordiazepoxide ranging from 10.0 to 175 mg/kg were administered twice per day for a period of 5 wk. At doses from 10.0 to 40.0 mg/kg, scores of withdrawal signs were greater than those with vehicle and increased with increasing dose. At doses from 80.0 to 175 mg/kg, scores of withdrawal signs were also directly related to dose; however, severity increased to an appreciably greater extent with increasing dose. Thus, the dose-effect curve for chlordiazepoxide withdrawal severity was biphasic, with an inflection point at around 40.0 mg/kg, and a greater slope at higher doses.

Swain (1065) studied chronic administration of relatively low doses of diazepam to rhesus monkeys. Groups of three monkeys were maintained on either 0.125 or 0.25 mg/kg/6 h s.c. diazepam for a period of 5 mo, after which withdrawal signs were monitored for a 10-day period. Signs of withdrawal included twitching, tremor (higher dose only), irritability, peculiar posture, and abdominal tenderness. These signs first appeared after 24 h, were most frequent between 48 and 72 h, and slowly subsided by the tenth day following drug discontinuation. Signs were generally more frequent, more intense, and longer lasting after chronic administration of the higher dose (see figures 1 and 2). According to the classification of withdrawal magnitude by Yanagita and Takahashi (1194), the withdrawal in the study by Swain would be classified as mild.

ii. Effects of duration of treatment. Boisse et al. (107) studied the effect of duration of chlordiazepoxide treatment using the chronically equivalent dosing technique. Withdrawal severity was scored following 7 to 35 days of twice-daily administration of doses that were adjusted to produce a specific degree of ataxia; the average final doses ranged from 175 to 435 mg/kg. At the end of treatment periods of 7 to 28 days, withdrawal was graded as moderate, with about 12 of 20 withdrawal signs obtained per subject. At the end of treatment periods of 35 days, withdrawal was graded as severe; the average number of withdrawal signs was 14.5. In a subsequent study, Boisse et al. (106) reported a reliably observed withdrawal syndrome following a single 450-mg/kg dose of chlordiazepoxide.

iii. Comparisons of different benzodiazepines. Martin et al. (719) compared dependence in rats following administration of diazepam, N-desmethyldiazepam, and oxazepam, each given i.g. in four doses amounting to 133 mg/kg/day. Subjects given N-desmethyldiazepam were not overtly sedated during treatment; however, 25% of these subjects died during the course of treatment. Subjects given oxazepam showed a decrease in eating during the course of treatment, and about 50% of the subjects that reached the final dose died. The intensity of the withdrawal syndrome, as rated by observers, was greatest for diazepam, since certain signs were less frequent in the N-desmethyldiazepam and oxazepam subjects. Onset of the withdrawal syndrome was most rapid in the subjects treated with oxazepam.

McNicholas and colleagues studied the development of physiological dependence in the dog following chronic administration of lorazepam, diazepam (745), or N-desmethyldiazepam (746). Drugs were administered i.g. through gastric fistulas. Doses of diazepam and lorazepam were increased daily until the dogs began to lose weight, and the doses were stabilized at levels that allowed the animals to maintain their body weight. The dose of diazepam was 58 to 60 mg/kg/day; of lorazepam, 100 mg/kg/day; and of N-desmethyldiazepam, 16 mg/kg/day. Each drug was given in four divided doses each day. The benzodiazepines were discontinued for 3 days every 2 wk. The withdrawal signs that developed were similar for the three drugs and included tremors of the extremities and of the body, twitches and jerks, "hot-foot" walking, and stiff-legged walking. There were differences in the time course of withdrawal from the different drugs, with signs of withdrawal appearing later in dogs treated with diazepam (peak at 64 to 80 h) or N-desmethyldiazepam (peak at 38 to 72 h) as compared with those treated with lorazepam (peak at 10 to 20 h). The N-desmethyldiazepam withdrawal signs were generally more frequent than were diazepam withdrawal signs; lorazepam withdrawal signs were the least frequent. Convulsions occurred following discontinuation of diazepam and N-desmethyldiazepam, but not following discontinuation of lorazepam. Despite the fact that N-desmethyldiazepam produced the most severe grade of withdrawal, the dogs showed no sedation or ataxia during chronic administration of this drug.

Physiological dependence to clonazepam has also been demonstrated in dogs. After discontinuation of 3 to 7 wk

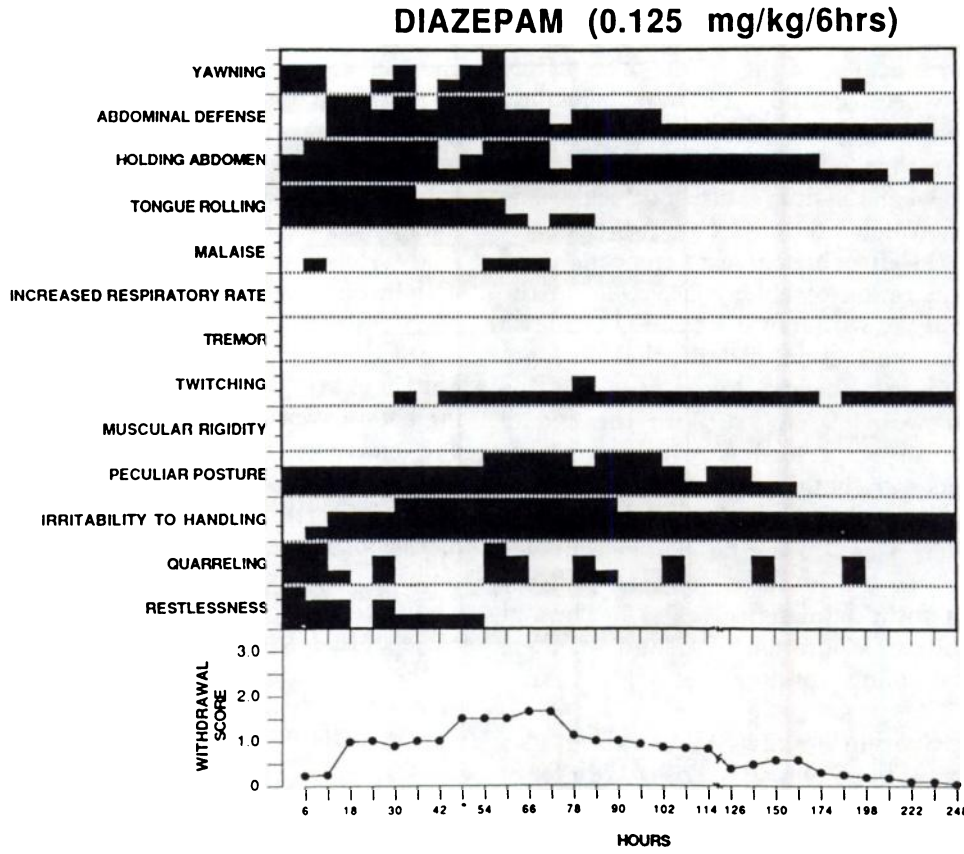

FIG. 1. Time course of various withdrawal signs observed in three rhesus monkeys following a 5-mo period of treatment with diazepam at a dose of 0.125 mg/kg/6 h. Methods of delivering drug and observing withdrawal signs were similar to those described by Seevers and Deneau (992) and Villarreal (1115). At each observation time point, each sign was judged as present or absent by trained observers. The *upper portion* of the figure indicates the number of subjects exhibiting each sign at each time point; the *lower portion* indicates the average of subjective scores of the severity of withdrawal that were assigned to each subject. Both the frequencies of various signs and the average withdrawal score were maximal between 48 and 72 h after termination of drug treatment. Note that some of the signs persisted in at least one subject for the duration of the 248-h observation period; however, the average subjective severity score had returned to near zero by 198 h after the drug was discontinued.

of twice-daily oral administration of 0.5 mg/kg of clonazepam, dogs developed hyperthermia, weight loss, and listless behavior (980). The threshold for pentylenetetrazol-induced convulsions was also decreased (981). Signs peaked on day 2 following drug discontinuation and had disappeared by day 8. Schütz (987) mentioned withdrawal signs in dogs that had received 2.5 to 80 mg/kg of clobazam for 6, 12, or 16 mo.

The most extensive comparisons of dependence on different benzodiazepines have been conducted by Yanagita and colleagues; some of these studies have been reviewed (1178). Withdrawal intensity was graded as mild, intermediate, or severe according to criteria used (1194) for grading barbiturate withdrawal. Mild withdrawal was indicated by apprehension, hyperirritability, mild tremor, anorexia, and piloerection. Intermediate withdrawal was indicated by aggravated tremor, muscle rigidity, impaired motor performance, retching or vomiting, and weight loss of at least 10%. Severe withdrawal was indicated by convulsions, delirium ("hallucinating behavior, nystagmus, dissociation from the environment"), and hyperthermia of greater than 1.5°C. It was not clear how many of these signs needed to be present in order for the grade to be assigned.

Drugs were typically administered i.g. for a 4-wk period; dose levels were sometimes increased after the first week. A 1-wk withdrawal observation was followed by administration of the drug at even higher doses for another 4 wk, followed by a second 1-wk withdrawal observation. Four rhesus monkeys were usually studied with each drug.

With one exception, in the tests conducted by Yanagita and colleagues, withdrawal was graded as either intermediate or severe in at least 1 of 4 subjects. Severe withdrawal was observed in at least 2 of 4 subjects after 8 mg/kg/day of alprazolam (1201), 113 mg/kg/day of chlordiazepoxide (1195), 16 mg/kg/day of clorazepate (1188), 8 to 20 mg/kg/day of diazepam (1195, 1191, 1181, 1179), 30 mg/kg/day of nimetazepam (methylnitrazepam, 1199), or 4 mg/kg/day of triazolam (1187); and in at least one of four subjects after 24 mg/kg/day of clobazam (1202), 120 mg/kg/day of cloxazolazepam (1197), 20 mg/kg/day of estazolam (1200), 60 mg/kg/day of lorazepam (1198), or 36 mg/kg/day of mexazolam (1180).

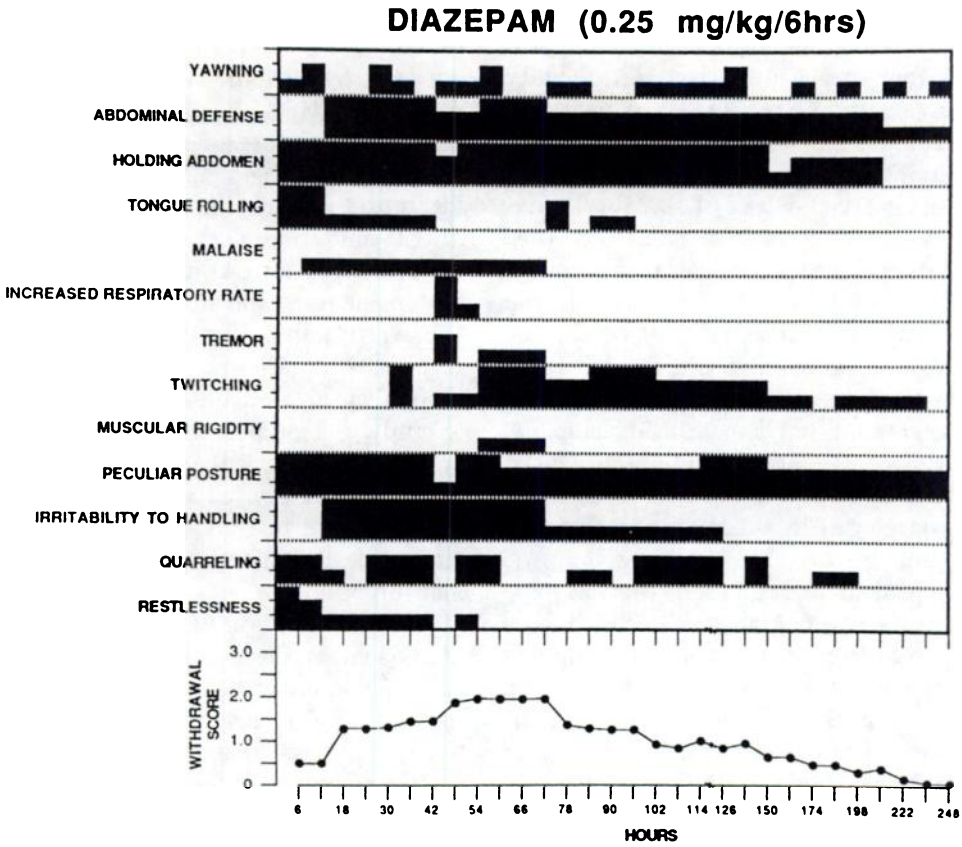

FIG. 2. Time course of various withdrawal signs observed in three rhesus monkeys following a 5-mo period of treatment with diazepam at a dose of 0.25 mg/kg/6 h. Details are as in fig. 1. Both the frequencies of various signs and the average withdrawal score were maximal between 48 and 72 h after termination of drug treatment. Note that some of the signs persisted in at least one subject throughout the 248-h observation period; however, the average subjective severity score had returned to near zero by 222 h after the drug was discontinued. Compared to effects at the lower dose (fig. 1), individual signs occurred more frequently and lasted longer during withdrawal from this dosing regimen.

Intermediate withdrawal was observed after 6 mg/kg/day of clonazepam (1190), 16 mg/kg/day of clorazepate (1188), 6 mg/kg/day of fludiazepam (1186), 8 mg/kg/day of flunitrazepam (1184), 3 mg/kg/day of flutoprazepam (1189), 480 mg/kg/day of halazepam (1192, 1181), 48 mg/kg/day of haloxazolazepam (1193), 16 to 30 mg/kg/day of nitrazepam (1181, 1185, 1179), 60 mg/kg/day of oxazolam (1195), 16 mg/kg/day of prazepam (1196), 64 mg/kg/day of quazepam (1181), or 64 mg/kg/day of zopiclone (1185, 1179).

The same investigators (1183) also studied lormetazepam at doses of 16, 128, and 192 mg/kg/day, which represent, respectively, 4, 32, and 48 times the doses minimally effective for sedation in normal rhesus monkeys. No withdrawal signs were observed after administration of the lowest of these doses, and only mild withdrawal was observed after administration of the two higher doses. It might also be noted that a dose of 256 mg/kg produced only incomplete reversal of signs of barbital withdrawal (table 1).

In a similar study, Kubota et al. (615) examined withdrawal after 4 wk of midazolam (0.9 mg/kg/day), triazolam (0.09 mg/kg/day), or pentobarbital (60 mg/kg/day), each administered i.v. in three divided doses. Withdrawal signs were observed in 1 of 4 monkeys given triazolam and 3 of 4 subjects withdrawn from pentobarbital. Weight loss was also observed in the pentobarbital subjects. After another 4 wk of doses one third higher, withdrawal signs were observed in 1 of 3 subjects treated with midazolam, 2 of 3 subjects treated with triazolam, and 3 of 4 subjects treated with pentobarbital. Weight loss was also observed in the triazolam and pentobarbital subjects.

Caution should be exercised in interpreting the findings of the studies described above with regard to the relative potentials of these compounds to produce dependence. First, there was no systematic attempt to compensate for differences in the potencies or durations of action of the various drugs. In some cases, the daily doses administered were over 1000 times the doses minimally effective for sedating normal monkeys. For other drugs, the daily doses were between one and 3 times the minimally effective doses. Further, there was no systematic attempt to compensate for different durations of action of the different benzodiazepines; different degrees of dependence may develop if a drug is active continuously as opposed to intermittently.

Stockhaus and Bechtel (1050) gave doses of brotizolam

and diazepam that were comparable in terms of their effects on motor coordination and locomotion. Each drug was administered to four rhesus monkeys, starting at 0.6 mg/kg/day of brotizolam and 1.5 mg/kg/day of diazepam, each given in three equal doses. The doses were increased until definite and similar effects on motor coordination and locomotion were observed. Doses of 16.2 mg/kg/day of brotizolam and 40.5 mg/kg of diazepam were then administered for 28 days. This represented nearly equieffective doses of these drugs, but was a much higher multiple of the human therapeutic dose of brotizolam than of diazepam. These doses, given in divided form, produced round-the-clock impairment in locomotor activity to which tolerance did not appear to develop. On the first day of drug discontinuation, mild, intermediate, and severe withdrawal signs, as defined by Yanagita and Takahashi (1194), developed in the monkeys that had been given brotizolam. Slightly less severe withdrawal signs developed, and peaked on day 3 following diazepam discontinuation. Serum levels of diazepam declined more slowly than did those of brotizolam following drug discontinuation, which may account for the differences in severity and in time to peak withdrawal effects in the two groups of monkeys. Daily doses of 0.6 and 1.8 mg/kg of brotizolam for 30 days did not produce any effects on motor coordination and did not result in withdrawal signs on drug discontinuation. A daily dose of 5.4 mg/kg for 30 days produced impairment of motor coordination; only a few withdrawal signs were observed on discontinuation of this dose.

In a subsequent study, Stockhaus (1049) compared the dependence that developed following chronic i.g. administration of brotizolam, diazepam, nitrazepam, and triazolam. The dosing regimens were selected on the basis of the human therapeutic doses of the drugs and for the first 4 wk were 2 mg/kg twice daily for brotizolam and triazolam and 10 mg/kg twice daily for diazepam and nitrazepam. During the second 4-wk period of drug administration, the dose of brotizolam and of triazolam was increased to 3 mg/kg twice daily, and the dose of diazepam and of nitrazepam was increased to 15 mg/kg twice daily. These doses of brotizolam, diazepam, and triazolam produced nearly equivalent effects on motor coordination (the effect of triazolam was greater during the first 2 wk, but decreased to comparable levels after that). The effects of nitrazepam on motor coordination were more profound, and two of the five monkeys receiving nitrazepam died of cardiovascular complications. Triazolam was the only drug to which tolerance appeared to develop. The drugs had markedly different durations of action. The monkeys had recovered much more from one daily dose of brotizolam, prior to administration of the second daily dose, than monkeys receiving their first daily doses of diazepam or nitrazepam; the duration of action of triazolam appeared to be greater than that of brotizolam, but less than that of nitrazepam or diazepam.

Discontinuation of brotizolam or nitrazepam produced few withdrawal signs. Brotizolam withdrawal signs began within 24 h following drug discontinuation and had disappeared by the fourth day. Nitrazepam withdrawal signs peaked on days 2 and 3 and declined over the next 7 days. Much more severe signs followed discontinuation of triazolam. The signs of triazolam withdrawal had a fast onset and declined over a 3-day period following drug termination. Diazepam withdrawal was also graded as severe, reaching a maximum on days 2 and 3 of drug discontinuation and slowly declining until day 5.

b. WITHDRAWAL INDUCED BY BENZODIAZEPINE ANTAGONISTS. With the development of specific benzodiazepine-receptor antagonists (502, 69), it became possible to study precipitation of withdrawal in subjects dependent on benzodiazepines in the same manner in which naloxone-precipitated withdrawal is studied in subjects dependent on opioids. Cumin et al. (211) reported the effects of administration of the benzodiazepine antagonist flumazenil to mice, rats, cats, and squirrel monkeys after administration of diazepam, lorazepam, triazolam, or midazolam. Flumazenil, given to rodents after chronic administration of benzodiazepines, produced hypermotility, decreased respiration, exophthalmus, hyperreactivity, clonic seizures, hypertonus, and salivation. Somewhat different signs were noted in the other species. Many of the signs observed in rodents were similar to those noted after cessation of benzodiazepine administration in other studies (e.g., refs. 949, 107, and 718).

In addition to studies with rodents (e.g., refs. 743, 329, and 105), precipitated withdrawal has been studied in several other species. Precipitated withdrawal has been observed in primates after treatment with diazepam (684, 1124, 378, 211), lorazepam (211, 626), or triazolam (211, 615, 396, 628); however, withdrawal was not observed following administration of flumazenil in animals treated with midazolam (211, 615). Withdrawal has also been observed in cats after administration of lorazepam, triazolam (211), diazepam, and flurazepam (932, 933) and in dogs after administration of diazepam (745) and clonazepam (980). A variety of withdrawal signs has been observed in the different species following antagonist administration, including convulsions (e.g., refs. 211, 745, and 684) and changes in postures (684) and locomotion (745, 743). Changes in EEG recordings were observed in rats given clonazepam (50 mg/kg/day) for a month and then given CGS-8216 (802). EEG changes were also reported in dogs that were given flumazenil after administration of 32 mg/kg/day of N-desmethyldiazepam i.g. for more than 2 wk (747). Some changes in electrical activity in the brain occurred in the absence of any behavioral changes, whereas some EEG changes occurred in the presence of increased agitation, head movement, biting, or lip movement. A grand mal seizure was also observed.

Increases in plasma corticosterone were observed in rats given the benzodiazepine antagonist CGS-8216 following 8 days of daily administration of 1 or 5 mg/kg of

diazepam. The increase in corticosterone was more prolonged in rats receiving the higher dose of diazepam (269) and may be a correlate of withdrawal.

As with opioid dependence (187), the concurrent administration of agonist and antagonist has been reported to inhibit the development of dependence. Guarino et al. (410) reported that physiological dependence to chlordiazepoxide was slightly attenuated in the rat if each administration of the drug (75 mg/kg, twice daily for 5 wk) was followed, 2 h later, by administration of 25 mg/kg of flumazenil.

i. Comparisons of spontaneous and precipitated withdrawal. Several studies have compared the syndrome of precipitated withdrawal with the syndrome of withdrawal after abrupt termination of benzodiazepine administration. McNicholas and Martin (742, 743) studied the effects of administration of flumazenil to rats maintained on a maximally tolerated dose of diazepam (133 mg/kg/day administered i.g. in four divided doses, roughly one every 6 h). The precipitated withdrawal syndrome was somewhat different from that resulting from drug discontinuation. Signs such as "explosive awakening," increased hostility, and decreases in body weight were observed during natural withdrawal but not after administration of flumazenil. Moreover, precipitated withdrawal, which was graded as maximal following administration of 15 mg/kg of flumazenil, was graded as substantially less severe than the maximum effect obtained following termination of drug administration. Similar results were reported for precipitation of withdrawal in diazepam-dependent rats using the benzodiazepine antagonist CGS-8216. The withdrawal signs increased with increasing doses of i.g. CGS-8216, up to a dose of 5 mg/kg, at which point the withdrawal signs plateaued (744).

Boisse and colleagues have compared withdrawal precipitated by flumazenil and withdrawal induced by drug deprivation following different chlordiazepoxide regimens in rats (101). The two withdrawal syndromes were generally similar, but differed with respect to presence or absence of some signs. Severity of precipitated withdrawal (as rated by observers) was similar at 435 and 75 mg/kg twice daily, and similar in rating to withdrawal following discontinuation of treatment with 75 mg/kg twice daily. Scores for severity of withdrawal were greatest following discontinuation of the higher dose of chlordiazepoxide.

Rosenberg and Chiu (931) studied precipitation of withdrawal by flumazenil in cats treated for 35 days with 5.0 mg/kg/day of i.g. flurazepam. Doses of 2.0 to 100 mg/kg of i.g. flumazenil resulted in a withdrawal syndrome characterized by tremor, twitching, increased respiration, muscle rigidity, piloerection, pupil dilation, and a decrease in eating. The graded severity of withdrawal did not appear strongly dependent on the dose of flumazenil used to precipitate withdrawal. Interestingly, the authors reported that, following 5 wk of flurazepam treatment at this dose, there were no obvious signs of withdrawal when drug treatment was discontinued.

Scherkl and Frey (980) saw a rapid development of timidity, hyperthermia, and leg tremor in dogs given flumazenil following 1 to 6 wk of daily administration of clonazepam. The withdrawal signs did not become more intense with increasing duration of clonazepam administration. A more pronounced withdrawal syndrome was observed with drug discontinuation after 7 wk of clonazepam administration, as was described earlier.

Lukas and Griffiths (684) found that administration of flumazenil (5.0 mg/kg) i.m. promptly precipitated withdrawal in baboons maintained on diazepam (20 mg/kg/day) i.g. as a continuous infusion for 7 or 35 days. The withdrawal syndrome precipitated by the antagonist was much more intense than that following drug-deprivation withdrawal. Certain signs, e.g., lip smacking, nausea, retching and vomiting, lying on cage floor, rigid bracing, and convulsions, were seen soon after administration of the antagonist, but were not observed after abrupt diazepam discontinuation. In a subsequent study (627), deprivation-induced withdrawal in baboons maintained on the same dose of diazepam for several months resulted in a long-lasting (2-mo) decrease in food intake. Typical signs of withdrawal (e.g., tremor, vomiting, or convulsions), however, were either absent or infrequent. Precipitated withdrawal in these subjects was similar to that observed previously, with convulsions or myoclonic jerks at the highest dose of the antagonist (32 mg/kg).

Withdrawal signs similar to those observed with diazepam were observed in baboons given a continuous i.g. infusion of lorazepam at 20 mg/kg/day for 7 days and then given 5 mg/kg of flumazenil. Baboons maintained for 26 or more days on this dose of lorazepam and then abruptly discontinued from the benzodiazepine showed tremor and decreased food intake. These signs began within 2 days after drug discontinuation and were still evident at 9 days after drug discontinuation (626).

ii. Effects of antagonist dose. A few studies have examined precipitated withdrawal as a function of dose of the antagonist. In an initial study of flurazepam-treated cats (931), there was a poor correlation between the rating of withdrawal (as judged by observers) and dose of flumazenil. In a subsequent study (932, 933), the rating of withdrawal was found to be maximal at a dose of 25 mg/kg; higher doses only prolonged the duration of action.

McNicholas and Martin (743), using a complex method of determining overall severity of withdrawal involving a weighting of individual signs, found a plateau in the dose-effect curve of flumazenil at doses of 15 mg/kg and higher. At higher doses, the time course of withdrawal was lengthened without changes in the rated severity of withdrawal. A similar dose-effect curve for the antagonist CGS-8216 was found in a subsequent study, where CGS-8216 was equipotent with flumazenil over the range of doses studied (744). A study of the two antagonists in

dogs dependent on N-desmethyldiazepam found effects of flumazenil related to dose, with no indication of a plateau at higher doses. Additionally, flumazenil was more potent than CGS-8216 (719).

Lamb and Griffiths (627) examined effects of dose of flumazenil on frequencies of individual withdrawal signs in baboons treated for several months with a continuous i.g. infusion of diazepam (20 mg/kg/day). Frequencies of some signs were directly related to dose, whereas frequencies of other signs showed a plateau or even decreased at the highest doses. In a subsequent study (629), these authors compared dose-effect curves of flumazenil with those of CGS-8216. Both antagonists precipitated signs of withdrawal; however, flumazenil produced those signs more rapidly and with clearer relation of dose and effect. As in the previous study, frequencies of some signs were directly related to dose of flumazenil, whereas frequencies of other signs showed a plateau or even decreased at the highest doses. Interestingly, at doses of the two antagonists producing comparable effects on particular signs, CGS-8216 was lacking effects on certain other signs (see also ref. 106). These results indicate some differences between the two antagonists other than differences in bioavailability.

The results of the studies by Lamb and Griffiths (627, 629) are reminiscent of those with opioids (86, 87) showing different dose-effect relations for different withdrawal signs. Since individual signs that comprise the total withdrawal score show different dose-effect functions, it is not surprising that studies employing composite withdrawal scores should find a plateau at the higher doses of the antagonist. The finding of such a plateau suggests only that individual withdrawal signs may not be a function of the same variables; it should not be taken to suggest that withdrawal "severity" changes directly in accord with the composite withdrawal score.

iii. Effects of dose of benzodiazepine agonist. Lukas and Griffiths (685) evaluated the degree of dependence, as indicated by flumazenil-induced withdrawal signs, that developed in baboons exposed to different doses of diazepam. Diazepam was continuously infused intragastically at doses of 0.125, 0.25, 0.5, 1.0, or 20 mg/kg/day for 7 days. The number of withdrawal signs observed in the baboons increased as a function of dose of diazepam. The frequency of withdrawal signs was greater than control levels after 7 days of administration of 0.25 mg/kg/day. At the lower dose, the frequency of withdrawal signs was not greater than control levels. Some withdrawal signs showed consistent increases with increasing dose of diazepam, while other signs increased and then decreased at higher doses.

In studies of flurazepam dependence in cats, Rosenberg et al. (932, 933) found that the rated severity of the withdrawal syndrome following administration of flumazenil to cats that had received 5 to 20 mg/kg/day of flurazepam for 35 days was only slightly greater than that in cats that had received 1 mg/kg/day of flurazepam for 35 days.

Boisse et al. (105, 101) indicated that withdrawal scores precipitated by 25 mg/kg of flumazenil were greatest at doses of chlordiazepoxide of 40 and 75 mg/kg twice daily, and lower at doses of 20 mg/kg twice daily. The withdrawal scores at the higher dose were approximately 120% of those occurring at the lower dose of chlordiazepoxide. In a subsequent study, examining a wider range of chlordiazepoxide doses (408), the withdrawal severity scored was directly related to the dose of chlordiazepoxide up to a dose of 450 mg/kg twice daily.

iv. Effects of duration of benzodiazepine treatment. Lukas and Griffiths (685) evaluated the degree of dependence, as indicated by flumazenil-induced withdrawal signs, that developed in baboons under conditions of different durations of diazepam exposure. Diazepam was continuously infused intragastrically at a constant daily dose of 20 mg/kg/day for 1 h or 1, 3, 7, or 35 days. The number and intensity of withdrawal signs observed in the baboons increased as a function of duration of diazepam administration. A frequency of withdrawal signs greater than control levels was demonstrated on the third day of treatment in baboons that had not previously received benzodiazepines. At a dose of 0.25 mg/kg, withdrawal signs were observed after 7 days of administration; shorter exposure durations were not examined at the lower dose. Some withdrawal signs showed consistent increases with increasing durations of diazepam exposure, while other signs increased and then decreased. Interestingly, three baboons that had been exposed to benzodiazepines 50 to 180 days prior to the experiment developed dependence more quickly (within 1 day of exposure to 20 mg/kg/day) than the benzodiazepine-naive baboons. This suggests that the development of benzodiazepine dependence may be contingent on prior drug exposure; similar suggestions have been made on the basis of human studies, as discussed in the following section.

Rosenberg and Chiu (932, 933) administered flumazenil to cats following 1 to 70 days of chronic treatment with 5 mg/kg/day of flurazepam. The withdrawal syndrome observed was given the highest score at 35 and 70 days of treatment, an intermediate score at 3 and 7 days of treatment, and was given the lowest score after 1 day of treatment.

Acute dependence on chlordiazepoxide was demonstrated in rats given a single dose of 450 mg/kg of chlordiazepoxide and challenged with flumazenil after 4 to 148 h (105, 106, 858). Precipitated withdrawal signs were observed between 28 and 100 h, with a peak at 76 h after chlordiazepoxide injection. Several other doses (10 to 150 mg/kg) of chlordiazepoxide were examined for the capacity to induce acute dependence in the rat. In these studies, effects of flumazenil were assessed only at 4 h after injections. The maximally scored withdrawal

syndrome was obtained after the 75-mg/kg dose; however, it was not observed as reliably after this dose as at 76 h after 450 mg/kg. Comparisons of the time course of acute withdrawal and agonist actions of chlordiazepoxide revealed that, in order to observe some withdrawal, there must be some remaining effect of the agonist and that the dose of antagonist must reverse those effects. Comparison of the acute withdrawal syndrome with that observed after chronic drug treatment indicated some differences in the constellation of signs observed. These data suggested to the investigators that acute and chronic dependence may be induced by two different mechanisms or may be due to pharmacokinetic limitations on the effects of the antagonist.

v. Comparisons of different benzodiazepine agonists. McNicholas and Martin (745) compared the effects of 25 mg/kg of CGS-8216 in dogs maintained on diazepam (60 mg/kg/day) and lorazepam (100 mg/kg/day). Compared to dependent subjects that were not treated with the antagonist, none of the withdrawal signs was substantially altered in the lorazepam-dependent subjects, whereas the frequencies of two signs (gross body tremor, "hot-foot" behavior) were increased in the subjects dependent on diazepam.

Boisse et al. (102, 409) compared flumazenil-precipitated withdrawal following administration of N-desmethyldiazepam or diazepam at various dose levels. This study was conducted in rats since, unlike the dog (see ref. 746), in this species both drugs are eliminated relatively quickly, and diazepam is eliminated without an accumulation of N-desmethyldiazepam; thus it was possible to compare dependence on these two compounds without ambiguity as to the possible effects of N-desmethyldiazepam as a metabolite of diazepam. The withdrawal precipitated after treatment with both drugs was directly related to dose, with a greater slope for the diazepam dose-effect curve. When withdrawal was assessed as a change from values obtained before administration of the antagonist, it was determined that a larger change occurred with diazepam than with N-desmethyldiazepam. This difference between the two drugs was accounted for by a greater withdrawal score prior to antagonist administration in the subjects treated with N-desmethyldiazepam. There were also some differences in the particular signs that were observed after the antagonist was administered. These data suggested to the investigators that N-desmethyldiazepam may have been acting as a partial agonist.

3. Summary and discussion. Information about the development of physiological dependence on benzodiazepines typically supports the understanding of physiological dependence that has been garnered from studies of this phenomenon with opioids, barbiturates, or ethanol. The general rules suggest that withdrawal signs are more frequent or of greater magnitude (*a*) following administration of higher doses, i.e., doses with greater effects; (*b*) following treatment for longer periods of time; and (*c*) with continuous rather than periodic drug administration. Further, the expression of withdrawal is more rapid, and signs may be more frequent or of greater magnitude, when the drug is removed from the receptor quickly, i.e., when a short-acting drug has been administered.

Some interesting exceptions to these rules have been observed in some studies with benzodiazepines. For example, McNicholas et al. (745, 746) reported more severe withdrawal from N-desmethyldiazepam than from diazepam or lorazepam in the dog, although N-desmethyldiazepam did not produce as much intoxication as did the other two benzodiazepines. On the other hand, Stockhaus (1049) observed a greater behavioral effect in the monkey during chronic administration of nitrazepam, as compared with that associated with other benzodiazepines, but much less severe withdrawal signs when nitrazepam administration was discontinued. This suggests that, among the benzodiazepines, there may be exceptions to the typical positive relation between the degree of initial effect and the degree of dependence development. While these findings may suggest novel effects of benzodiazepines, other drug classes may also present exceptions to these general rules of physiological dependence. Likewise, some benzodiazepines may have effects independent of their actions at benzodiazepine receptors, that may not contribute to, may interfere with, or may obscure the development of physiological dependence; such effects may also occur with other drug classes.

There have also been some conflicting results in studies of precipitated withdrawal. Some studies have found the syndrome precipitated by antagonists to be rapid, dependent on the dose and duration of administration of the agonist, and related to the amount of agonist administered (e.g., ref. 685). However, others (931–933, 744, 743) have found a plateau in the severity of withdrawal signs, as rated by observers, following administration of an antagonist. Inconsistencies among these studies may be reconciled by examining effects on individual withdrawal signs. Individual signs are often affected differently during the course of withdrawal or as a function of antagonist dose.

There have been occasional observations that withdrawal following drug deprivation was more severe than that following antagonist administration (743, 744, 980). These findings have been interpreted as reflecting a difference between opioid and benzodiazepine dependence, since with opioids precipitated withdrawal is often more severe than withdrawal following drug discontinuation. It should be remembered, however, that the severity of a withdrawal reaction may depend on several factors, and that the severity of withdrawal from a given drug can depend on factors such as the interval between the last dose of the agonist and the administration of the antagonist (e.g., refs. 101, 932 and 933), as well as the

dose of the agonist or antagonist (e.g., refs. 101, 105, 685, and 627). The differences in precipitation of withdrawal may also be peculiar to the particular benzodiazepine antagonists that have become available for study. The severity of the withdrawal reaction precipitated may depend to a large degree on the kinetics of the individual antagonists studied. Obviously, we will understand precipitated withdrawal better when more is known about the interaction between benzodiazepine agonists and their antagonists, as well as about the direct effects of the antagonists alone in various species.

The results of antagonist-precipitated withdrawal should not be interpreted necessarily as simple effects of benzodiazepine withdrawal. At least some of the signs observed may be effects of an interaction between the antagonist and the benzodiazepine agonist. It is important to continue to compare the signs that result from drug deprivation and those that develop following antagonist administration, as the differences in these syndromes have yet to be fully characterized.

There is some evidence suggesting that the benzodiazepines may vary in their potential to produce physiological dependence in animals. However, it is quite difficult to be certain that the drugs have been given under comparable conditions, taking into consideration differences in duration of action and potency. A shorter-acting drug must be given more frequently than a longer-acting drug to assure effects over a comparable portion of the day. Also, if degree of dependence is equal, more severe withdrawal should be expected from a shorter-acting drug, since it is removed from the body more rapidly. In order to evaluate possible differences in dependence capacity among benzodiazepine agonists, it is necessary to use methods that permit chronic administration of equivalent doses (e.g., refs. 107 and 949); such studies should also include comparisons of drugs across a range of effects. Also, in order to eliminate some of the differences among the benzodiazepines with respect to their durations of action, comparisons of withdrawal signs should be done under conditions of antagonist-induced withdrawal. Experiments of this kind should attempt to account for the possible sequelae of agonist-antagonist interactions that are not due to withdrawal. Since differences in withdrawal signs produced by drugs of the opioid, as well as of the barbiturate, class can usually be attributed to differences in the kinetics of the agonist-receptor interactions, this should be the first area explored in seeking to explain possible differences among the benzodiazepines with respect to their capabilities to produce dependence.

C. Studies in Humans

1. Physiological dependence to high doses. Early measurements of the signs of benzodiazepine withdrawal and of the time course of withdrawal following chronic administration of chlordiazepoxide were made by Hollister et al. (486). The study was conducted on 11 chronically ill psychiatric patients who were given 300 to 600 mg/day for 2 to 6 mo, doses that were 3 to 40 times the currently recommended therapeutic dose. The signs that developed following abrupt discontinuation of these doses included depression and aggravation of psychoses. Insomnia, agitation, and loss of appetite also developed in some patients and, in two patients, major convulsions were observed. The most severe withdrawal occurred between the fourth and eighth days, apparently starting on about day 2 and continuing through day 10.

In a subsequent study of the efficacy of diazepam in schizophrenics, Hollister et al. (484) noted that, of 25 patients with mild schizophrenia who were given 20 to 80 mg of diazepam daily for 6 wk, one developed withdrawal signs on drug discontinuation. This patient had been on the highest dose of diazepam. Unfortunately, neither the nature nor the time course of withdrawal was described. Six of 13 more severely ill patients, who received 120 mg/day of diazepam for 3 wk following lower doses for the preceding 3 wk, showed withdrawal signs when switched to placebo. Again, the details of these withdrawal signs were not specified, although one patient had a convulsion on day 8.

A more recent description of diazepam withdrawal signs following prolonged administration of high doses has been provided by Mellor and Jain (758), who evaluated the syndrome in 10 men who had taken diazepam for periods ranging from 3 to 14 yr. The range of doses taken in the 6 mo prior to drug termination was 60 to 120 mg/day. This is considerably lower than the doses administered by Hollister in his first study, although still more than twice the typical therapeutic dose. Six of the subjects in this study had originally received diazepam for anxiety, two for alcoholism (they had not used alcohol for 2 yr prior to this study), one for involutional depression, and one for muscle spasm. The diazepam was abruptly discontinued (no diazepam placebo was given), and the patients were observed and evaluated every 8 h until they were discharged. The authors reported three major groups of clustered signs. Group A signs, which occurred throughout the 6 wk of observation, were severe in the first 2 wk and increased again in the third to fourth weeks of withdrawal; these signs included tremor, anorexia, sweating, anxiety, agitation, insomnia, and myoclonus. Group B signs peaked during the first withdrawal week and declined throughout the remainder of withdrawal; these signs, resembling those seen in alcoholic delirium tremens, included tachycardia, hypertension, clouding of consciousness, and hallucinations. The Group C signs showed a maximum intensity at about 3 wk and a smooth decline after that; they included perceptual disorders, such as paresthesias and hypersensitivity to light and sound, as well as muscular and abdominal pain and depersonalization.

The signs in Groups A and B were very similar to signs observed in withdrawal of alcohol and barbiturates. Those in Group C appeared to be distinct from alcohol

and barbiturate withdrawal signs. Although insomnia, agitation, and anorexia were reported in both this study of Mellor and Jain (758) and the study of Hollister et al. (486), the studies had little else in common with respect to the descriptions of withdrawal. Even the time courses described (10 days in the Hollister study, and more than 5 wk in the Mellor and Jain study) were remarkably different. These discrepancies suggest that there may be considerable variability in the signs that develop on benzodiazepine withdrawal. It is also possible that some of the later signs may be subtle and subject to investigator interpretation; this emphasizes the importance of the use of double-blind evaluation and careful experimental design.

2. *Physiological dependence to therapeutic doses.* Covi et al. (207) evaluated withdrawal from chlordiazepoxide in anxious patients being treated with anxiolytic drugs. In the first of two studies, a comparison was made of the effects of withdrawal of placebo, 1600 mg/day of meprobamate, and 40 mg/day of chlordiazepoxide. Each condition was maintained for 16 wk; placebo was then given to all patients for 1 wk. Patients were interviewed periodically, and one interview was conducted at the end of the week of placebo administration. Patients also completed a symptom checklist that included symptoms characteristic of withdrawal. Some patients receiving chlordiazepoxide but not meprobamate or placebo showed an increase in withdrawal signs (not described in detail) following discontinuation of medication. Those who did, however, were found to be those who had been receiving benzodiazepines, barbiturates, or meprobamate prior to the initiation of this study.

In order to study the effect of prior medication on the subsequent development of chlordiazepoxide withdrawal, Covi et al. (206) then evaluated withdrawal signs following 4 mo of administration of 40 mg/day of chlordiazepoxide, which had been preceded by at least 1 mo of administration of either phenytoin or phenobarbital. As the earlier study had suggested, those receiving prior medication with phenobarbital developed considerably more withdrawal "distress" than those receiving prior medication with phenytoin, although there was a slight increase in "distress" in these latter patients as well.

Although these studies utilized a more generalizable patient population than did Hollister et al., they unfortunately measured withdrawal signs at only a single time period (1 wk) following drug discontinuation. Thus it could not be clearly determined if the symptoms observed represented actual withdrawal, which would have dissipated through time, or symptom recrudescence, which would have been unlikely to disappear in these anxious patients. However, the fact that all patients had similar levels of withdrawal distress following administration of chlordiazepoxide, while those pretreated with phenobarbital showed greater withdrawal distress after 1 wk of placebo, indicated actual withdrawal rather than symptom recurrence in these subjects. The authors did not clearly specify the type or incidence of symptoms that developed on drug withdrawal. Thus, unfortunately, it is not feasible to compare specific symptom development in these experimental studies of large numbers of patients with the many case reports of withdrawal in individual patients.

a. INTERVIEW AND QUESTIONNAIRE SURVEYS. These studies by Covi and colleagues alerted investigators to the possibility that dependence could develop to therapeutic doses of benzodiazepines. One approach to evaluate this possibility was to conduct interview and questionnaire studies to discover the types of problems encountered by benzodiazepine users when they stop taking their medication. Maletzky and Klotter (698) used an interview technique to determine the incidence of withdrawal signs in 50 patients who had been using prescribed diazepam for relatively long periods. Of these, 24 had attempted on their own to stop taking diazepam abruptly. On the basis of subjects' recall, the investigators found that all of these 24 subjects had experienced at least mild withdrawal symptoms; 19 described moderate to severe symptoms. The average daily diazepam intake had been 16 mg, but many of the subjects had also been taking other minor tranquilizers. The mean duration of intake was reported as 26 mo, although it is unclear from the report what periods of drug use had preceded attempts to terminate medication.

An interview technique was also used by Khan et al. (576) to determine the incidence of dependence to benzodiazepines in a general-practice patient population. They questioned 40 patients who met the criteria of using benzodiazepines as their sole psychotropic medication for 6 mo or more. Doses were within the therapeutic range. Seventeen % of these patients spontaneously reported that they had experienced difficulties when they abruptly terminated benzodiazepine administration. Among the signs reported were extreme anxiety, depression, and sleep disturbances. These may have been effects of symptom recurrence, a possibility that Hallstrom and Lader (427) attempted to rule out in their questionnaire study, which examined the development of new symptoms as well as the recurrence of old symptoms.

In this study (427), information on benzodiazepine withdrawal was based on questionnaires sent to members of the Phobics Society in Great Britain. The questionnaire requested information on tranquilizer use and included questions about the effects observed when medication was stopped. There were obvious limitations in the study design, since members of the Phobics Society are probably not representative benzodiazepine users; there was also a self-selection bias because only those requesting the questionnaire and then returning it could be included in the study (the report did not specify the percentage of members who agreed to participate). Eighty-two % of the subjects who reported using benzodiazepines (mean daily doses of 12.5 mg of diazepam, 25

mg of chlordiazepoxide, 3 mg of lorazepam, or 30 mg of medazepam) had tried to reduce or eliminate their drug intake. A return of symptoms was reported by over 90% of these respondents. Forty-two % indicated that, in addition to the return of anxiety, one or more new symptoms—most commonly shakiness, dizziness, sleep disturbance, impaired concentration, and nausea—emerged when medication was halted. Twenty-six % noted that more than one of these new symptoms appeared on drug discontinuation, and it was this group that the authors considered to be showing actual withdrawal.

Patients who presented a prescription for diazepam at the pharmacy of a large Veterans Administration clinic served as subjects in a study by Haskell et al. (440). Of 400 such patients, 210 agreed to complete several questionnaires about their use of benzodiazepines. Of these, 71% indicated that they took benzodiazepines daily, and 66% reported "continuous" use of the drug since it was initially prescribed for them; for 75%, this had been at least 2 yr previously. Of 108 subjects reporting that they had tried at some time to stop using this medication, 93 reported a return of old symptoms and 19 reported the development of different, new symptoms. This suggests that benzodiazepine withdrawal developed in some of these long-term users.

b. PLACEBO-CONTROLLED STUDIES. Perhaps the clearest information regarding the possibility that benzodiazepine dependence can develop in patients using therapeutic doses for the treatment of anxiety came from a number of placebo-controlled studies of such patients. Bowden and Fischer (125) evaluated 23 anxious psychiatric outpatients who had been taking diazepam (30 mg/day for 16 patients, 20 mg/day for 6 patients, and 15 mg/day for 1 patient) for at least 6 mo prior to the study. Under double-blind conditions, half of the patients continued taking the dose they indicated they had been taking, and the other half were given placebo tablets. After 2 wk, patients were asked about any symptoms they had experienced during the previous 2 wk. Anxiety was evaluated with the Hamilton Anxiety Rating Scale (HARS) at the beginning, midpoint, and end of the 2-wk study. The results indicated that, while anxiety increased in patients receiving placebo at both 1 and 2 wk, the actual withdrawal scores were lower than those of patients on active drug. The authors interpreted these results as suggesting that withdrawal is infrequent in patients taking diazepam chronically at therapeutic doses.

Twenty-four outpatients with anxiety disorders served as subjects in another study of discontinuation of therapeutic doses of diazepam (637). They reported daily and long-term (at least 6 mo) ingestion of diazepam (mean dose, 17 mg/day; mean duration, 5 yr). The patients were given either 10, 15, 20, or 30 mg/day of diazepam for 1 wk, and they were then either abruptly changed to placebo, reduced gradually in dose by 5 mg/wk, or maintained on their preassigned dose. Weekly evaluations were made of anxiety levels (HARS), symptoms of withdrawal (certain items of the Hopkins Symptom Checklist), and mood (POMS). There was no difference among the three groups on these measures prior to drug deprivation. Blood levels of diazepam and desmethyldiazepam were also taken, in part to check for compliance; results indicated that the subjects took their medications as assigned. These patients had fairly high levels of anxiety at the beginning of the study; the patients who were changed abruptly to placebo had higher anxiety levels at the end of the study (3 to 7 wk after abrupt withdrawal) than did the patients maintained on diazepam. Since this difference was not seen at earlier withdrawal times, it was attributed to symptom recrudescence rather than withdrawal. No evidence of withdrawal was seen among groups on the symptom checklist, and neither patients nor blinded raters could distinguish the maintenance from the withdrawal condition.

Although few subjects showed signs of withdrawal in these studies, a substantial number of similar experiments has demonstrated a benzodiazepine-withdrawal syndrome in patients taking therapeutic doses of these drugs. Tyrer et al. (1097) evaluated benzodiazepine withdrawal in all patients attending certain clinics who had been receiving only diazepam (average, 10 mg/day) or lorazepam (average, 4 mg/day) for at least the previous 4 mo, and who agreed to participate. Forty subjects were assigned to either placebo or propranolol for 2 wk and asked to rate themselves each day on items such as anxiety, tremor, nausea, and palpitations. The results are complicated by the fact that 7 of the 8 patients on lorazepam and 11 of the 32 patients on diazepam dropped out of the study, an effect that may have been due to the severity of withdrawal, as discussed on pages 283 and 284 below. Of the patients remaining in the study, 27% (6 of 22) were found to have experienced withdrawal, in that self-ratings of symptoms increased to more than 50% above baseline levels and then returned to lower levels.

Brown et al. (140) studied six subjects who had been taking 30 to 100 mg/day of chlordiazepoxide for periods ranging from 9 to 58 mo. The investigators maintained the subjects on their customary doses for 2 wk, abruptly changed them to placebo for 4 wk, and then returned them to medication for 4 wk. These manipulations were made under single-blind conditions. Three of the six subjects experienced anxiety, headache, insomnia, and depression following drug discontinuation. One was sufficiently uncomfortable that he was returned to medication after 1 wk, another after 2 wk. The time course of the symptoms of the third subject was not described, so it is unclear whether the signs observed were actually due to withdrawal or merely represented a return of symptoms present prior to medication.

A comparison of the effects of discontinuation of halazepam (120 mg/day in divided doses) or oxazepam (45

mg/day in divided doses) was reported by Pecknold et al. (854). Following a week of placebo administration, each drug was administered for 3 wk to 29 patients who had diagnoses of anxiety neurosis. Drug was abruptly discontinued in all patients; half of them received placebo. Withdrawal was indicated by the number of symptoms reported by subjects on a benzodiazepine withdrawal rating scale and also by scores on the HARS. A withdrawal syndrome that included insomnia, impaired concentration, depression, and muscle aching was described, peaking in the first week following drug discontinuation and declining to near zero levels in wk 7 and 8. These particular symptoms were seen in between 55 and 69% of the 29 subjects. There was no difference between oxazepam and halazepam in either the severity or incidence of the withdrawal reactions, despite the fact that halazepam has active metabolites and thus a much longer duration of action than oxazepam, which has no active metabolites.

Fontaine et al. (306) studied discontinuation of bromazepam or diazepam in 48 outpatients with generalized anxiety disorders. All but six of these patients had taken a benzodiazepine prior to the start of the study (some for over a year), and a 1-wk washout period preceded the daily administration of the test drugs (bromazepam, 18 mg; diazepam, 15 mg; or placebo). After 4 wk of drug or placebo administration, half of the subjects in each group were abruptly taken off their medications; in the other half, the drug was gradually discontinued over a 3-wk period. Dose changes were made under double-blind, placebo-controlled conditions. Both changes in anxiety and the development of new symptoms were evaluated following drug discontinuation. In the abruptly discontinued group, anxiety increased to levels above those shown during the washout period and by the placebo group. With gradual drug discontinuation, anxiety measures returned to but did not exceed predrug levels. New symptoms, suggestive of dependence, developed in conditions of both abrupt and gradual drug discontinuation, although the incidence of insomnia, gastric symptoms, and muscle spasms was higher in the abruptly discontinued group. The new withdrawal symptoms were less long-lasting than rebound anxiety, and both were suppressed by benzodiazepine administration. The incidence of withdrawal was not noted, but the most frequently observed sign, insomnia, developed in 62% of those whose drug was abruptly discontinued, and 36% of those whose drug was gradually discontinued.

Power et al. (883) administered diazepam at a dose of 15 mg/day to 21 subjects with a diagnosis of generalized anxiety disorder, who had not taken medication in the past 3 wk and had no prior history of continuous or prolonged benzodiazepine use. Under single-blind conditions, all subjects received placebo for 1 wk. Ten were then placed on 15 mg/day of diazepam, and the remainder continued to take placebo. A 6-wk period of medication was followed by a 2-wk period without drug. Anxiety ratings for both placebo and diazepam subjects decreased during administration of the medication; the anxiety scores of only the diazepam subjects increased following drug discontinuation. Withdrawal was indicated by the development of new symptoms and by the return of symptoms that had been reported prior to administration of diazepam. A greater number of patients who had been taking diazepam reported symptoms than did patients who had been taking placebo. This study suggested that even short-term administration of therapeutic doses of diazepam to relatively drug-naive subjects could result in dependence.

Tyrer et al. (1095) compared withdrawal signs that developed following discontinuation of 5 to 20 mg/day of diazepam or buspirone. Drug administration was continued for either 6 or 12 wk prior to discontinuation, but only those who had received diazepam for 6 wk showed withdrawal symptoms on the Comprehensive Psychopathological Rating Scale (CPRS). The incidence of these symptoms peaked at 2 wk after drug discontinuation and then declined. It was unclear why no withdrawal signs were observed in those taking diazepam for 12 wk.

c. WITHDRAWAL IN SELF-SELECTED SUBJECTS. There has been a number of studies of development of withdrawal symptoms in people who were selected for participation in the experiments because of suspected prior dependence to benzodiazepines. A group of ten patients requesting assistance in benzodiazepine withdrawal was evaluated by Hallstrom and Lader (426). The patients were continued on the dose of medication they claimed to have been taking (confirmed by measures of plasma levels) for 10 days. There were two dose levels, one a mean of 135-mg diazepam or diazepam equivalents, the other a mean of 20 mg of diazepam. (One of the four subjects in the high-dose group was taking chlordiazepoxide, and one was taking lorazepam and diazepam; diazepam equivalents were estimated for these subjects based on measures of receptor binding of diazepam and its metabolites in serum samples.) The medication was gradually withdrawn over periods ranging from 10 days to 7 wk, before, during, and after which several measures of withdrawal were taken. All subjects showed withdrawal, as indicated by temporary increases in anxiety, alterations in EEG measures, weight loss, and intolerance to noise and light. Interestingly, the withdrawal signs did not differ markedly between the high-dose group and the low-dose group. Since the low-dose group had apparently not taken the medication for a longer period than the high-dose group, these findings suggested the possibility that the severity of benzodiazepine withdrawal may not be directly related to amount of drug intake.

This study served as a pilot study for a series of reports by Petursson and colleagues on various aspects of withdrawal from low-dose, long-term benzodiazepine administration (865, 861–863). Petursson and Lader (867) presented a thorough description of these, or very similar,

studies of benzodiazepine withdrawal in 26 patients who reported taking therapeutic doses of various benzodiazepines regularly for periods ranging from 1 to 20 yr (mean, 7.7 ± 4.5 yr). Drugs used were diazepam (17 patients with a mean daily dose of 17.3 ± 6.9 mg), lorazepam (6 patients with a mean daily dose of 4.7 ± 2.5 mg), clobazam (2 patients each taking 30 mg/day), and oxazepam (one patient taking 90 mg/day). One patient was taking 2.5 mg of lorazepam plus 0.125 mg of triazolam daily. The drugs had originally been prescribed primarily for problems of anxiety, and most patients had been referred to the investigators because they wanted assistance in withdrawing from their medications. For all but five patients, drug discontinuation was carried out under placebo-controlled, double-blind conditions. The subjects were maintained on their prescribed drug for 2 or 4 wk while various baseline measures were obtained. The dose was then reduced by half for 2 wk, and then placebo was substituted completely for the drug.

Twenty-two patients completed the study. These subjects showed a variety of withdrawal signs during reduction and elimination of the medication. HARS scores increased sharply but transiently during withdrawal. Symptoms of anxiety, shaking, trembling, and muscular tension increased as rated on a bodily symptoms rating scale. Anxiety became severe in some patients, and a few reported feelings of depersonalization. Most patients experienced profound insomnia the first two to three nights of withdrawal. Nineteen patients experienced at least one sign that was considered indicative of withdrawal in that it was not typically associated with increased anxiety, i.e., was a "new" symptom. Interestingly, particularly in view of the reports of Hollister (486), four patients developed psychotic phenomena of either hallucinations or persecutory delusions.

Although most of the reported symptoms developing during withdrawal were related to the conditions for which the drugs had originally been prescribed and could have been considered symptom recrudescence, the authors concluded that they were most likely withdrawal phenomena. The increased anxiety and insomnia were relatively short-lived, decreasing while the subjects were still off medication.

In a recent, thorough evaluation of dependence to therapeutic doses of benzodiazepines, Busto et al. (150) evaluated a subject population that appeared similar to that of Petursson et al. (866). The 42 subjects were either self-referred, physician-referred, or had responded to newspaper or radio requests for "people concerned with their long-term benzodiazepine use." All had taken therapeutic doses of benzodiazepines daily for 3 mo or more, primarily for treatment of anxiety or insomnia. They all expressed concern about their use of benzodiazepines because they were having memory disturbances or other problems associated with use of the drugs, or because they had developed problems when they tried on their own to stop taking the drug. Subjects had used benzodiazepines for at least 3 mo, with a total cumulative exposure (i.e., the product of the average daily dose and total days of use) greater than 2700 mg of diazepam or its equivalent.

Under the conditions of the study, all patients continued taking their prescribed benzodiazepine for 2 wk and were then randomly assigned, under double-blind conditions, to take an equivalent dose of diazepam or to take placebo. The dose of diazepam (or placebo) was decreased at a rate determined in a contract between the subject and a therapist and averaged a 3.5-mg reduction per week over 5 to 6 wk. Subjects were asked to record on a checklist any symptoms that developed each day during this time; severity of symptoms was also recorded on a scale of 1 to 10. The subjects were permitted to take their originally prescribed benzodiazepine during the "tapering" procedure, but were asked to report such use; this use was also checked by urine screens.

The subjects who "tapered off" placebo administration (i.e., had their previous medication abruptly discontinued) developed more symptoms and symptoms of greater severity than did subjects who tapered off diazepam administration. Those receiving placebo also developed symptoms more rapidly than did those receiving decreasing doses of diazepam. In the latter subjects, the symptoms were fewer in number, less severe, and later in development. When drug was abruptly discontinued, subjects were more likely to take supplemental doses of their previous medication than were those receiving diazepam.

Withdrawal symptoms included signs that could be considered symptom recrudescence, i.e., fear, tension, and difficulty concentrating, but also included symptoms such as persistent tinnitus, involuntary movements, paresthesias, perceptual changes, and confusion, which had not occurred prior to benzodiazepine administration. Interestingly, the subjects shifted directly to placebo from shorter-acting benzodiazepines, such as lorazepam or oxazepam, developed withdrawal signs more rapidly, within the first day of placebo administration. Those who had been taking diazepam or flurazepam did not develop symptoms until day 5. The symptoms were not significantly more severe for those on shorter-acting benzodiazepines, but many more of these subjects dropped out of the study. Seven subjects dropped out during the withdrawal phase of the study; all of these had been taking lorazepam. This suggested that withdrawal from the shorter-acting benzodiazepines was more aversive than withdrawal from the longer-acting drugs.

d. DISCONTINUATION OF SHORTER-ACTING BENZODIAZEPINES. There have been other recent studies of withdrawal from shorter-acting benzodiazepines. Unfortunately, these reports frequently lacked critical information such as the dose of the drug given, the number of patients showing withdrawal, or the time course of withdrawal. A study mentioned earlier (1097) compared lor-

azepam withdrawal to diazepam withdrawal and found two indications of more severe withdrawal from lorazepam. One was that all but 1 of 8 lorazepam subjects dropped out of the study during the withdrawal phase, compared to 11 of 32 of the subjects who had been taking diazepam. The other was that the severity of lorazepam withdrawal in the one remaining subject (and in the others until they dropped out) was more marked than that occurring with diazepam withdrawal. These symptoms also developed much earlier in the lorazepam subjects (1098).

Bueno (144) reported preliminary data on 420 female psychiatric outpatients who had been drug free for at least 10 days. The subjects were assigned to one of eight drug treatment groups; one of the treatment groups received placebo, six received benzodiazepines of different durations of action, and one group received a non-benzodiazepine. The average duration of treatment was 28 days. When drug administration was stopped, there was an increase in signs such as anxiety, insomnia, motor agitation, etc., which were similar to the problems the patients had before treatment. Also, ataxia, gastrointestinal cramps, and dysphoria developed in some patients (number, unfortunately, not specified) on drug termination. These signs appeared more likely to develop in patients who had been receiving a shorter-acting benzodiazepine.

Pecknold and Swinson (855) conducted a study of patients with panic or phobic disorders. Patients were assigned to either alprazolam (dose not specified) or placebo for 8 wk and then underwent a process of gradual discontinuation of medication over a 4-wk period. Of 32 patients discontinued from alprazolam, 28% experienced panic attacks of greater frequency and severity than those experienced previous to treatment, indicating a rebound effect. Twenty-two % showed rebound anxiety. At least four patients developed new symptoms (e.g., blurred vision, muscle cramps) during the last week of tapered medication or the first week with no medication.

Cohn and Noble (184) observed 72 patients with anxiety disorders who were changed to placebo from as much as 4.5 mg/day of alprazolam or 9 mg/day of lorazepam after 32 wk of administration. They noted that 53% of the patients did not report any change during the 4-wk placebo period; 43% of the alprazolam and 53% of the lorazepam patients reported side effects (unspecified), and most of these dropped from the study during the placebo period. Nevertheless, the authors emphasized minimal withdrawal effects, though this finding was difficult to interpret due to the paucity of data presented.

Rickels et al. (920) compared the withdrawal symptoms that developed following administration of longer-acting benzodiazepines (diazepam and clorazepate) to those developing following administration of shorter-acting benzodiazepines (lorazepam and alprazolam). Subjects were 119 patients, most of whom were diagnosed as anxious or depressed. Sixty-eight % had been taking prescribed benzodiazepines for 5 yr or longer, 45% had been taking these drugs for 10 yr or longer, and 32% had been taking them for 15 yr or longer. The mean dose of diazepam was 15.2 mg/day; of clorazepate, 18.2 mg/day; of lorazepam, 3.9 mg/day; and of alprazolam, 2.7 mg/day. Forty-three of the patients had never tried to discontinue their medication. Of the 76 patients who had tried to discontinue benzodiazepines, only 3 reported that they had been able to do so without problems.

The subjects were allowed to continue taking their prescribed medications for 3 wk; then, under double-blind conditions, drug was abruptly discontinued for 65 of the patients. Withdrawal measures included physician observations or patient reports of increased severity of original symptoms or the development of new symptoms. Withdrawal was noted in 82% of both patients discontinued from short-acting benzodiazepines and patients discontinued from long-acting benzodiazepines. However, the withdrawal symptoms during the first week of drug discontinuation were more severe in patients who had been taking short-acting benzodiazepines, particularly with respect to changes in mood, somatic, CNS, sleep, gastrointestinal, and adrenergic symptom clusters on the Physician Benzodiazepine Withdrawal Checklist. Thirty-five % of patients discontinued from long-acting benzodiazepines dropped out of the study during drug discontinuation; 69% of those discontinued from short-acting benzodiazepines dropped out. This difference was not statistically significant. This study represents one of the best-controlled observations of withdrawal from long- and short-acting benzodiazepines and indicates that dependence is not more likely to occur with the shorter-acting drugs, but that withdrawal may be more severe following discontinuation of these drugs.

e. FACTORS PREDISPOSING TO DEPENDENCE. The patients in the carefully executed and controlled studies of Busto et al. (150), Hallstrom and Lader (426), and Petursson and Lader (867) were distinctive in that most of them showed some evidence of physiological dependence prior to the study. They had tried to abstain from taking their medication, had experienced symptoms such as anxiety and tremor, and had relieved these symptoms by resuming use of benzodiazepines. They were sufficiently interested in ceasing this medication that they had talked to their physicians and had been referred to the investigators. The critical questions are to what extent these subjects were representative of the general population of benzodiazepine users, and whether some physiological or psychological feature could be used to characterize them and others like them as "high-risk" patients.

These studies of withdrawal from therapeutic doses of benzodiazepines do not clearly answer the questions of how frequently these withdrawal reactions can occur, and what conditions may predispose to benzodiazepine withdrawal. In some studies (125, 637, 281), no withdrawal signs developed in the subjects, while in others (919, 1087, 576), withdrawal signs developed in a small

percentage of subjects, and in still others (149, 306, 426, 698, 867, 883), withdrawal was shown in all, or apparently a large majority, of the subjects.

Two studies attempted to isolate some of the factors that may contribute to the development of physiological dependence on benzodiazepines. Tyrer et al. (1096) evaluated 34 patients from 5 general-practice psychiatric clinics. (Five of the originally selected 41 patients dropped out before the end of the study, and 2 refused to give requisite blood samples.) Those selected for the study were current, regular users of 5 to 20 mg/day of diazepam and had been taking these doses for at least 3 mo prior to the initiation of this study. The subjects were told that their medication would be gradually reduced over a 3-mo period until they would be taking no tablets at all. They were divided into two groups, both of which were put on a standard dose of 0.2 mg/kg/day of diazepam for the first 2 wk of the study. Following this, under double-blind, placebo-controlled conditions, group A received half this dose of diazepam for 2 wk, one quarter this dose for 2 wk, and placebo tablets only for 6 wk; then tablet administration was halted. Group B was maintained on the standard dose of diazepam for a total of 8 wk and then dropped, first to half of this dose, then to a quarter of this dose, for 2 wk each; tablet administration was then halted for this group as well. All patients were given fewer tablets per day during the last 4 wk of tablet administration to give the appearance of reducing the dose of diazepam for both groups.

Symptoms of withdrawal were recorded by means of the CPRS, administered before the study and at 2-wk intervals throughout the study. Withdrawal reactions were indicated by either a temporary increase in symptoms over 50% above baseline levels or by the development of two or more new symptoms. A personality assessment scale was administered to a "close informant" of each subject, categorizing the subject as normal, schizoid, obsessional, passive-dependent, or sociopathic. Serum measures of diazepam and nordiazepam were also taken at intervals throughout the study.

A total of 44.4% of the subjects showed withdrawal reactions when the two withdrawal criteria were collapsed into a single criterion—the appearance of new signs that disappeared before the end of the study. Using the two criteria separately uncovered a small percentage of pseudowithdrawal reactions, typically increased anxiety, that developed while the dose and blood levels of diazepam were maintained. No pseudowithdrawal reactions were observed when the two criteria were collapsed into one. The symptoms that appeared included perceptual disturbances, insomnia, anorexia, depression, and depersonalization.

The data were analyzed to determine whether the occurrences of withdrawal were associated with age, sex, dose of drug at the time of withdrawal, duration of previous drug treatment, rate of fall of serum drug levels, or personality type. The only variable that showed a significant correlation with observations of withdrawal was that of personality type. Subjects with passive-dependent personalities were more likely to show withdrawal signs, while those with obsessional personalities were less likely to show withdrawal. A more thorough analysis indicated that subjects showing withdrawal had higher scores in lability, resourcelessness, sensitivity, and impulsiveness.

Rickels et al. (919) evaluated the effect of length of benzodiazepine administration and the effect of concurrent ethanol ingestion on the risk of developing dependence on benzodiazepines. Subjects were 129 chronically anxious patients. The study was divided into a 6-wk period of diazepam administration (15 to 40 mg/day; mean, 25 mg/day) followed by an 18-wk continuation phase. During the latter phase, under a double-blind, placebo-controlled design, subjects received either 18 wk of placebo (group 1), 8 wk of diazepam and 10 week of placebo (group 2), or 16 wk of diazepam and 2 wk of placebo (group 3). Less than half of the patients had been taking benzodiazepines prior to the start of this study, and these patients were fairly equally distributed among the three continuation groups. Assessment of drug effects and drug withdrawal effects was carried out by periodic administration of the HARS, the Covi Anxiety Scale, the HSC, and items from a withdrawal scale described by Covi et al. (206).

Considering only the 69 patients who had not used benzodiazepines before the start of the study, only 7 developed withdrawal symptoms on drug discontinuation. None of these were in group 1, i.e., those given diazepam for 6 wk. Four subjects developing marked withdrawal signs were in group 2, i.e., with 14 wk of diazepam administration; however, three of these four reported daily consumption of two drinks (or more) of alcoholic beverages. One subject in group 2 showed transient, mild withdrawal. One patient showing marked withdrawal was in group 3, i.e., receiving diazepam for 22 wk in the study. A second patient in this group showed limited withdrawal. This suggested that the likelihood of becoming dependent on therapeutic doses of benzodiazepines was quite low if the drugs were given for 6 wk or less, and that the chance of dependence development was only slightly increased with 14 or 22 wk of administration. Since the investigators reported that 48% of these chronically anxious patients maintained clinical improvement for several months after being shifted to placebo following 6 wk of diazepam administration, these findings indicated that this short period of administration was frequently effective and virtually always safe.

Evaluation of the data from patients who reported use of benzodiazepines prior to the initiation of the study showed that, of 21 patients who had taken benzodiazepines for more than 8 mo, 9 (43%) developed clear withdrawal signs and 3 developed mild withdrawal signs. No patients who had previously taken sedatives for 8 mo or less showed marked withdrawal signs; two patients

with less than 8-mo prior use showed transient withdrawal signs.

Taken as a whole, this study showed that there was virtually no risk of developing even mild dependence with intake of therapeutic doses of benzodiazepines for 6 wk or less. The chances of developing signs of withdrawal increased slightly with intake periods of between 3 and 8 mo, but became considerably greater if intake was longer than 8 mo. The concurrent use of ethanol with anxiolytic medication was very likely to increase the chances of developing physiological dependence.

f. REVIEWS OF BENZODIAZEPINE DEPENDENCE. Despite the fact that benzodiazepines have been used clinically for more than two decades, findings of mild physiological dependence in a fairly substantial percentage of subjects taking therapeutic doses have been reported only recently. A number of excellent reviews of this problem have been sparked by the case reports and controlled studies of this phenomemon. Lader (619) reviewed data from his and other laboratories and made the important points that physiological dependence can develop in subjects that have not escalated their drug doses, and that patients can develop dependence to benzodiazepines alone; no other "addictive" agents need accompany benzodiazepine administration. MacKinnon and Parker (692) described the benzodiazepine withdrawal signs and their time course. These reviewers emphasized that concomitant administration of alcohol or barbiturates could increase the likelihood of the development of benzodiazepine dependence, and that duration of therapy appeared to be more important than drug dose in contributing to the development of physiological dependence, at least within the therapeutic dose range. They also made a distinction between rebound insomnia and drug withdrawal; this distinction is discussed in some detail in the following section of this review and rejected as inappropriate.

Schopf (983) emphasized the interesting perceptual disturbances that developed in many instances of benzodiazepine withdrawal and raised the possibility that this symptom may be unique to withdrawal from these compounds. He joined others in suggesting that the duration of benzodiazepine administration might be critical in the development of physiological dependence and suggested that 1 yr might be the minimal time period for the development of dependence.

Owen and Tyrer (838) presented a thorough review of the literature on tolerance and physiological dependence to benzodiazepines. They noted that, while the number of prescriptions for benzodiazepines increased dramatically in the United Kingdom between 1961 and 1977, this did not indicate that the drugs were necessarily used to excess. They also noted that there was little evidence of significant tolerance to the clinical effects of benzodiazepines, and that patients rarely increased their doses over time. They found that withdrawal reactions, in the form of the appearance of new symptoms following termination of drug administration, indicated that physiological dependence to benzodiazepines could develop with relatively long-term administration of fairly high doses. These reviewers suggested that the minimal duration of treatment necessary to produce dependence was about 3 to 4 mo. They made the important point that dependence did not appear to develop in all patients taking benzodiazepines chronically for prolonged periods of time; thus, factors other than dose and duration of administration must be determinants of the development of withdrawal reactions.

Readers interested in other reviews of the literature on human physiological dependence on benzodiazepines might wish to refer to those by Greenblatt and Shader (382) and Petursson and Lader (864).

g. SUMMARY. The research evidence supports the claims that (*a*) physiological dependence to benzodiazepines does occur; (*b*) the withdrawal signs appear to be more severe if the dose level is high than if it is low; (*c*) dependence can develop to therapeutic doses if these doses are given for prolonged periods of time; (*d*) withdrawal signs develop more rapidly and may be more severe following chronic administration of shorter-acting, as opposed to longer-acting, benzodiazepines; (*e*) physiological dependence does not appear to occur in all people taking therapeutic doses for prolonged periods; and (*f*) concomitant or prior use of drugs such as barbiturates or ethanol may increase the likelihood of development of dependence to benzodiazepines.

A number of patients who had been taking benzodiazepines for long periods of time have reported that they experienced difficulties in attempting to reduce or terminate their medication. There was no evidence that this was associated with escalation of doses.

There is no clear consensus as to how long a person can continue taking benzodiazepines on a daily basis without developing dependence. The estimates vary from less than 6 wk to 1 yr.

3. Rebound insomnia. As described in the introduction to this section, the effects of withdrawal from narcotics and sedative-hypnotics often include rebound effects, i.e., temporary changes from baseline that are opposite to those initially produced by the drug itself. Several rebound effects have been associated with the benzodiazepines, including insomnia, anxiety (564, 883, 306, 167), and increases in excretion of monoamine oxidase inhibitor (861). There has been a reluctance on the part of some investigators to include rebound effects among the indications of physiological dependence on benzodiazepines (692). Others, in contrast, have suggested that the majority of withdrawal effects may be rebound effects (838).

The reluctance to accept rebound effects as withdrawal phenomena may be due to some extent to the desire to be conservative in the diagnosis of withdrawal, accompanied by the lack of assurance that the postdrug anxiety or insomnia observed is an actual rebound effect and not

simply symptom recrudescence. This position certainly has merit in the absence of good predrug baseline measures of the effects in question. In the studies of rebound insomnia, however, careful predrug baseline measures are almost always obtained, allowing precise descriptions of the direct effects of the drugs on the various sleep measures, and of the amount of rebound that occurs following drug termination. When sensitive measures reveal a definite rebound effect, it is appropriate to consider this genuine withdrawal, since these signs usually otherwise meet at least one of the criteria for the definition of withdrawal, as described in the introduction to this section; i.e., they are time limited. These signs may also meet the criterion specifying that they should be reversed by administration of a benzodiazepine, though the studies described here did not examine this possibility; we think it important that this question should be pursued.

Studies of the effects of administration of benzodiazepines have usually used subjects with insomnia and have evaluated the latency to fall asleep, the total sleep time, and, frequently, the time spent in the various stages of sleep before, during, and after several nights of bedtime drug administration. Rebound effects could potentially be observed with any of these measures, but the most frequently described effects were on sleep latency and total wake or total sleep time. Rebound insomnia, defined as a significant increase over baseline in EEG measures of sleep, was much more likely to develop with shorter-acting than longer-acting benzodiazepines, e.g., Bixler et al. (81).

Administration of midazolam, a short-acting compound, in doses of 20 or 30 mg for 1 or 2 wk resulted in rebound insomnia (562, 780). Rebound insomnia was not observed with 10-mg doses administered for 2 or 7 days (562, 341) or with 20-mg doses administered for two nights to normal subjects (341). Patients taking 20 mg of midazolam each evening for 1 wk were found to wake earlier in the morning than they had prior to drug administration. This phenomenon, labeled "early-morning insomnia," was considered to be potentially a form of rebound insomnia that developed during the night with drugs with short durations of action (563).

Triazolam, a short-acting benzodiazepine that is used clinically as a hypnotic, has been studied extensively in rebound insomnia paradigms. Rebound insomnia or early morning insomnia has been reported by several investigators using 0.25, 0.5, or 1.0 mg of triazolam for 4 to 21 days (559, 553, 563, 558, 1121, 1120, 5, 704). Pegram et al. (857) and Roth et al. (939) did not find rebound insomnia following 2 or 3 wk of nightly administration of 0.5 mg of triazolam. Both brotizolam and oxazepam, two short-acting benzodiazepines, produced increased sleep time or decreased wake time on administration, and significant insomnia over baseline on drug withdrawal (1111, 90). Studies of rebound insomnia with lormetazepam, a short- to intermediate-acting hypnotic, showed a significant rebound effect on drug discontinuation (4, 81, 556, 835). Lorazepam, with a duration of action close to that of lormetazepam, produced a rebound insomnia on some of the early withdrawal nights (977, 555). Temazepam, which has a half-life of approximately 10 h and a short-duration active metabolite, has not been shown to produce significant increases in insomnia following drug discontinuation in two studies measuring sleep electrophysiologically (79, 774). A study of the effects of 30 mg of temazepam on subjective reports of sleep indicated that the drug produced considerable amounts of sleep disruption on withdrawal following four consecutive nights of administration. No subjective report of sleep disruption occurred upon discontinuation of administration of 10 or 20 mg (468).

Fosazepam itself has a very short duration of action, but has at least two active metabolites, one of which, desmethyldiazepam, has quite a long half-life of elimination. Allen and Oswald (10) found no rebound insomnia following 3 wk of administration of fosazepam. Viukari et al. (1118) also reported no rebound insomnia problems in psychogeriatric patients given 60 mg of fosazepam each night for 1 wk. In this study, data were obtained by nurses' ratings of patients' sleeping patterns.

Studies of rebound insomnia following administration of flunitrazepam have produced mixed results. Bixler et al. (78) found significant rebound effects following administration of 1 but not 2 mg/kg of flunitrazepam for 1 wk. Sharf et al. (974) reported significant rebound effects with flunitrazepam as measured by total wake time on the first withdrawal night. Measures of wake time had returned to baseline by the 12th night after drug discontinuation.

Hindmarch and colleagues have reported two studies using subjective evaluations of sleep by noninsomniac subjects. These subjects were given 1 mg of flunitrazepam or placebo and asked to evaluate certain aspects of their sleep in the morning. During the four nights of drug administration, the subjects reported falling asleep more rapidly, although the subjective quality of their sleep was unchanged. During three withdrawal nights, there was no significant alteration in either of these parameters (469). A similar study by Hindmarch et al. (477) revealed a nearly identical absence of rebound effects following administration of 1 mg of flunitrazepam for four consecutive nights.

Diazepam, not normally given as a hypnotic, was shown to be effective in this regard, and to produce continued decreases in total wake time during the first 5 days following discontinuation (975). The administration of nitrazepam for 10 wk to a population of older patients was shown by Adam et al. (3) to increase the amount of time these subjects slept. A significant decrease in sleep time was recorded on drug withdrawal, however. Interestingly, the time to fall asleep was not altered during this time, but intervening wakefulness was markedly increased.

No change in the percentage of time asleep was observed in volunteer college students following 3 days of nightly administration of 5 mg of nitrazepam (824). Neither did withdrawal of 5 mg of nitrazepam in normal volunteers after administration for four consecutive nights result in signs of rebound insomnia as measured by subjective reports of sleep (469). These latter two studies, showing no rebound insomnia on withdrawal of nitrazepam, used a considerably shorter period of administration than did the study by Adam et al. in which rebound insomnia did develop. This suggests that rebound insomnia following nitrazepam may not develop until the drug has been administered for more than 3 to 4 days.

Flurazepam is one of the most frequently prescribed benzodiazepine hypnotic medications. It has a long half-life by virtue of a long-acting active metabolite. Its effects on sleep have been studied extensively. It maintained effectiveness as a hypnotic over fairly prolonged periods of administration and showed carryover effects when administration was discontinued (560, 554, 565, 1120, 90, 4). No rebound has been reported, even 2 wk after drug discontinuation (557, 81). Identical results have been reported with quazepam, a newer hypnotic with direct effects that last even longer than those of flurazepam (561, 563, 557, 558, 704, 81).

The information reviewed here tends to support the hypothesis that rebound insomnia following discontinuation of drug administration represents a true sign of withdrawal and thus indicates physiological dependence. This statement, however, requires qualification. It is important, first of all, to note that insomnia is a complex disorder and takes various forms (76, 512). In addition, sleep difficulties for a particular individual may not occur nightly, but may vary depending on external and internal conditions. Thus, the amount of sleep an "insomniac" patient will have on a given night is subject to considerable variability. Most of the studies reviewed used subjects diagnosed as insomniac or subjects who considered themselves to be poor sleepers. The subjects were rarely described more fully, and it is impossible to know the nature and extent of their sleep difficulties. Careful inspection of the data makes it clear that there was a large amount of variability in amount of sleep of these subjects, despite the fact that measures of variability are very infrequently reported. Large differences in the predrug levels of sleep in different groups are not uncommon. A further indication of substantial variability appears in the frequent failure to find statistically significant differences among conditions characterized by distinct changes in sleep levels. In the face of this variability, it is important for investigators and readers to pay close attention to the statistical test results in these studies; the graphs and figures presented often do not reflect this variability and may therefore be misleading.

One might expect a high frequency of prior use of medications in these insomniac patients, but the drug histories of the subjects were rarely elaborated. The type of medication used prior to a given study and the duration of use could influence the development of rebound insomnia following benzodiazepine medication.

In the introduction to this section of the review, physiological dependence was described as more likely to develop with longer-acting drugs. It is important to note that, on the contrary, rebound insomnia appears to occur more readily following administration of shorter-acting drugs. This interesting discrepancy should not be construed as detracting from the usefulness of rebound insomnia as a measure of withdrawal. In fact, it emphasizes the sensitivity of EEG-recorded sleep measures as indicators of drug effects and drug withdrawal. As mentioned earlier, EEG changes have been reported during barbiturate withdrawal when clinical signs were unchanged. Sensitive measures can reveal withdrawal following a single administration of drugs such as ethanol (748), while less sensitive measures may not reveal an effect unless withdrawal follows several days or weeks of chronic administration. This indicates that rebound insomnia is a sign of mild withdrawal, probably part of a continuum that progresses to the more profound insomnia reported following discontinuation of chronic, high-dose administration of benzodiazepines (e.g., ref. 759). Since it is a sign of mild withdrawal, the longer-acting hypnotics, such as flurazepam and quazepam, which effectively produce a gradual reduction in dose, should block the appearance of this sign. It is likely that administration of a benzodiazepine antagonist to subjects who had been taking flurazepam or quazepam for several weeks would reveal the fact that mild dependence to these drugs had indeed developed. It has been shown that administration of flumazenil 24 h after a single dose of flunitrazepam (0.03 mg/kg) resulted in increased reports of anxiety in three of six subjects (244). Thus, the conclusion that dependence does not develop with administration of the longer-acting benzodiazepines is not warranted, although the evidence reviewed does support the conclusion that rebound insomnia does not develop with administration of the longer-acting benzodiazepines.

The final and most important issue to be raised by these observations of rebound insomnia following discontinuation of administration of therapeutic doses of short- to intermediate-acting benzodiazepines is whether this effect leads to increased use, or more frequent use, of these drugs. Studies of barbiturates have shown that, when the drug is taken to relieve insomnia, drug-metabolizing enzymes are induced and the duration of action of the drug is thereby shortened. The barbiturates also decrease rapid eye movement (REM) sleep and, when the drug effect is worn off, or administration is stopped, REM sleep rebounds accompanied by bad dreams and nightmares. Thus, some believe, intake of the barbiturate is increased to overcome the shortened effects and the consequences of the REM rebound. Barbiturate-induced

insomnia is a clinically described phenomenon that can result from chronic administration of barbiturates to treat insomnia (76, 512). Such a description has not been presented for the benzodiazepines. These drugs do not induce metabolizing enzymes, nor do they generally result in REM rebound when their intake is reduced or stopped. Thus, two major problems associated with the use of barbiturates to treat insomnia are avoided by the use of benzodiazepines. The development of rebound or early morning insomnia could lead to continued ingestion of benzodiazepines. It is thus important that physicians prescribing short-acting benzodiazepines as hypnotics should encourage their short-term use and warn the patients of the temporary consequences of stopping the medication. It might be appropriate to substitute a longer-acting benzodiazepine for a shorter-acting one if the patient or the physician wants to stop the hypnotic, and if the patient is willing to accept some residual daytime sedation as a likely consequence of using these agents.

4. Case studies. Reports of benzodiazepine withdrawal frequently appear in the literature. These reports often take the form of a short letter and give limited information. Case studies have several disadvantages. They rarely provide any information as to the incidence of the described phenomena. They are usually uncontrolled observations of withdrawal. The drug-use history is typically also uncontrolled and based on a report by the subject, who may not accurately recall the drugs or doses he has been taking. It is often not clear whether the signs described represent recurrence of earlier symptoms or genuine withdrawal. In addition, the cases that merit reporting are usually those deemed exceptional in some respect, and the significance of these exceptional aspects is often obscure.

Primarily because of these limitations, it would not serve the interests of this review to describe a large number of case reports. Secondly, because of limitations inherent in information retrieval, no such listing can be exhaustive. [For a listing of illustrative case reports, the interested reader may wish to refer to Marks (see appendix 1 of ref. 714).]

Nevertheless, case studies cannot safely be ignored. They may provide the first clue to a phenomenon that should be more thoroughly investigated. In this light, and in order to illustrate the manner in which a case study can be conducted and documented to provide significant and valuable information about the syndrome of benzodiazepine dependence and withdrawal, one case study deserves more thorough description. This report (1158) of a double-blind, placebo-controlled study of a single patient has contributed much to the description of the course and symptoms which might be expected during benzodiazepine withdrawal.

The subject was a 32-yr-old man who had been taking 15 mg of diazepam for 6 yr for mild anxiety. He was referred to the authors because he had experienced unpleasant symptoms when he tried to reduce his dosage. The study was designed so that for 4 days he continued to receive his drug in the hospital and then was placed on placebo (double-blind) for 4 days, followed by another 4 days on diazepam and a final 21 days on placebo. He was evaluated daily for withdrawal signs, anxiety, and depression. Very few symptoms were noted during the periods of diazepam administration. During the first withdrawal period, a number of signs developed. They included, in the second day, anxiety, blurred vision, and dizziness, and, by the fourth day, extreme anxiety and irritability, diaphoresis, gross tremor, mild incoherency, insomnia, tinnitus, and hypersensitivity of auditory and olfactory senses. Within 30 min of a 5-mg dose of diazepam, all of these symptoms improved remarkably. During the second withdrawal phase, the above-mentioned symptoms reappeared, accompanied by visual sensory distortions and disorientation. The symptomatology was evident for 15 days, followed by continued improvement on days 16 through 22.

This study is especially helpful as a point of comparison for other case studies with respect to the type of symptoms and time course observed. It also provides striking evidence of withdrawal from therapeutic doses of diazepam, as supported by the more extensive investigations described earlier. Taken together with other case reports in the literature [e.g., those described by Marks (714)], these studies indicate that signs of withdrawal following termination of therapeutic doses of benzodiazepines include tremor, diaphoresis, anxiety, insomnia, and depersonalization, signs that might be expected with withdrawal from alcohol or other sedative-hypnotics. Unique signs of auditory and olfactory hypersensitivity are also reported quite frequently. Reports of convulsions and delirious responses are quite infrequent in studies of withdrawal from therapeutic doses, though they have been noted following administration of high doses for relatively long periods of time (486).

D. Summary and Discussion

1. Studies in animals. Animal studies have shown that, at high doses, all benzodiazepines studied are capable of producing physiological dependence. There have been some findings of variation in the signs of withdrawal from different compounds; however, it is not clear from any of the research conducted that the compounds vary qualitatively with respect to their relative potential to produce physiological dependence nor with respect to the nature of the withdrawal observed after drug discontinuation. Primary dependence studies have provided some suggestions that physiological dependence on benzodiazepines may diverge from the pattern of physiological dependence associated with other drug classes, i.e., opioids and barbiturates. Only a few studies have examined the potential of benzodiazepines to produce physiological dependence at low doses, i.e., doses analogous to those used for therapy in humans; these studies have

demonstrated some degree of withdrawal from chronic administration of such doses.

2. Studies in humans. Only a few of the large number of marketed benzodiazepines have been studied for their potential to produce physiological dependence in humans. In general, the findings of these studies parallel those of the animal studies; that is, they have demonstrated that physiological dependence can develop to high doses of benzodiazepines, and that mild dependence may develop in many patients who take therapeutic doses of benzodiazepines, on a daily or nearly daily basis, for prolonged periods. It is not yet clear what proportion of patients receiving therapeutic doses of benzodiazepines are at risk of clinically significant withdrawal from these drugs, nor is there sufficient information to establish whether there may be specific time and/or cumulative dose thresholds beyond which the risk of physiological dependence is increased.

A number of studies have indicated that rebound insomnia develops after discontinuation of hypnotic treatment with benzodiazepines. This phenomenon has some of the characteristics of withdrawal. It is more readily seen following treatment with the shorter-acting compounds than with the longer-acting compounds; this may be due to the fact that effective doses of the longer-acting agents are eliminated more gradually.

There have been some suggestions that certain factors may predispose to the development of physiological dependence on benzodiazepines or may augment such dependence. Some evidence from both animal and human studies has implicated a history of prior or concomitant exposure to other CNS depressants, including ethanol, as a possible predisposing factor. Unfortunately, this evidence in human studies has generally relied on drug-use histories provided by patients, a poor source of precise information. Animal research represents the most promising approach to precise exploration of this possibility.

3. Research considerations. At present, there is no definitive evidence of differences among the benzodiazepines with respect to their relative potentials to produce physiological dependence. This may be due in part to the difficulties inherent in studies attempting to demonstrate unequivocal quantitative differences in dependence. Basic pharmacological considerations have indicated that, in order to assess the relative probability that different drugs will induce dependence, subjects should be affected by the drugs to a comparable degree and for a comparable period of time. Thus, for such a comparison of benzodiazepines, their different durations of action must be taken into account, both during drug administration and during drug termination. Shorter-acting drugs must be given more frequently than longer-acting drugs, preferably using a chronically equivalent dosing procedure, whereby specific, equal levels of effect of the drugs compared are maintained around the clock. It is not necessary to use the highest tolerable doses; in fact, it is important to observe the development of dependence on low doses of various benzodiazepines, since this mimics more closely the dependence that develops to therapeutic doses in humans. In addition, there is a need to conduct studies in which acute effects of different benzodiazepines are maintained by the chronically equivalent dosing procedure; this type of experiment may also allow inferences regarding the associations among acute effects and dependence development.

Since longer-acting drugs are likely to produce less intense withdrawal, due to their "self-tapering" action, comparisons of withdrawal between drugs with different durations of action can be complicated. One procedure that can be used effectively to make this comparison is to give a long-acting drug chronically, and then substitute a short-acting drug for a few days before drug discontinuation. The long-acting drug should then be metabolized during the period of administration of the short-acting drug; and this period of administration should be sufficiently brief that there is little likelihood that dependence might develop to the short-acting drug itself. Thus it should be possible, when the short-acting drug is discontinued, to attribute the ensuing withdrawal to the dependence produced by administration of the long-acting drug (e.g., see ref. 104).

The benzodiazepine antagonists can also be helpful in evaluating the dependence potential of drugs with different pharmacokinetics. By producing an immediate withdrawal syndrome, an antagonist can temporarily "equalize" the durations of action of different agonists and thus allow an appropriate comparison of the intensities of withdrawal. Studies of this kind, however, should not neglect the possibility that the antagonist itself may produce signs apart from those that result from dependence, and that precipitated withdrawal might also differ in other ways from withdrawal produced by drug discontinuation.

In studies of benzodiazepine withdrawal in general, it is important to examine the effects of a wide range of doses. The interest of assessing the nature of withdrawal is better served by recording all signs that might be considered relevant to withdrawal than by measuring only single signs. It is also important to report changes with reference to individual withdrawal signs, rather than to report change on the basis only of composite scores.

4. Clinical considerations. When patients who have developed dependence on therapeutic doses of benzodiazepines abruptly stop taking these drugs, the withdrawal phenomena that develop include increased anxiety and insomnia. Other signs, such as alterations in taste and smell sensations, jitteriness, and tremor, may develop as well; but it is likely that increases in anxiety are primarily responsible for the difficulties found in stopping drug administration, particularly among patients who originally received a benzodiazepine to treat anxiety.

The studies that have demonstrated that physiological

dependence on benzodiazepines can develop following administration of therapeutic doses have also indicated that this dependence is not usually accompanied by a tendency to increase dosage; rather, patients appear more likely to want to reduce or terminate their use of the drugs. Although these observations are consistent with experimental research in self-administration, which has found no reinforcing effects of benzodiazepines in normal or anxious subjects (see section II above), they do not represent the results of rigorous measures of drug-taking behavior. Thus, neither these studies nor self-administration experiments have directly assessed whether benzodiazepines may acquire reinforcing effects as the result of the development of physiological dependence; it will be important to obtain reliable information on this question in order to evaluate the clinical significance of physiological dependence on benzodiazepines.

IV. Adverse Behavioral Consequences of Benzodiazepine Use

A. Introduction

As discussed in the general introduction (page 254), our definition of the abuse liability of drugs requires consideration of the drugs' potential to alter behavior in a manner detrimental to the individual or his social environment. An important influence on this definition, and on the approach taken in this review, was a WHO publication titled "Assessment of Public Health and Social Problems Associated with the Use of Psychotropic Drugs" (21), to which readers might wish to refer.

This section of the review addresses evidence regarding behavioral changes associated with the use of benzodiazepines. Some of the studies reviewed assess how these drugs alter performances on laboratory tests of "psychomotor skills" and "memory." This research may provide an indication of the mechanisms by which benzodiazepines alter behavior and may thus provide a basis for predicting how drugs will affect behavior under more routine conditions.

Other studies reviewed in this section focus more directly on the influence of benzodiazepines on behavior in situations more typical of those actually encountered by the patients for whom these medications are prescribed. Both the experimental and epidemiological studies reviewed here address the effects of benzodiazepine use on the risk of accidents. The majority of these studies have considered the risk specifically of automobile accidents; however, there have been some studies addressing the risk of other types of accidents.

Finally, this section considers several studies that have addressed the influence of benzodiazepine use on various aspects of social behavior, including subjective well-being and interpersonal relations.

B. Effects of Benzodiazepines on "Psychomotor Performance"

Ideally, it would be possible to design laboratory studies that assess the effects of benzodiazepines on human behavior such that the results would bear directly on the likelihood that these drugs lead to alterations in behavior outside the laboratory. Such predictability requires that the behavior studied in the laboratory is under the same functional control as the behaviors to be predicted outside the laboratory. The various laboratory procedures that have been utilized in studies of psychomotor performance are intended to measure some "psychomotor skill" or psychological process presumed to "underlie" an important behavior that occurs outside the laboratory, e.g., driving an automobile. Unfortunately, there is no clear evidence that effects of drugs on performances in these laboratory tests are predictive of performances outside the laboratory (cf. refs. 632 and 631).

As was the case for previous reviews (741, 1162), the present survey of the literature did not result in a basis for classification of types of performances affected by the various drugs. Therefore, as in previous reviews, the literature was surveyed and, in order to give some indication of the generality of the results, the frequencies with which the most commonly studied drugs produced effects were tabulated. Only those studies using appropriate predrug or placebo controls were included. We attempted to exclude studies reporting previously published results or preliminary reports of data presented more fully in later publications. Each dose comparison within a study was included; i.e., if a study examined more than one dose or examined the same dose twice, it contributed two dose comparisons to the tables. The tables were designed to indicate whether the drugs tested were found to produce effects, and whether the effects occurred at therapeutic doses or at doses above the therapeutic range. An effect on performance was indicated if the study reported a statistically significant effect, or, in the absence of statistical tests, if the effects shown appeared significant. Unless otherwise noted, the route of administration was oral.

The present review is far from comprehensive. There is an extensive literature on benzodiazepine effects on psychomotor performances, and space considerations alone preclude a comprehensive review. For other reviews of this literature, other than those mentioned above and in the following text, the reader may wish to refer to refs. 1164, 657, 1026, and 538.

The studies reviewed here were those that conducted similar tests on common drugs. Unfortunately, this approach is selective, in that it omits studies that used a novel procedure or investigated the effects of an infrequently studied drug. In several of the procedures employed, more than one parameter can be affected by the drug tested. For example, in the choice reaction procedure, a drug can affect the accuracy of the response as well as the reaction time. Many of the studies reported only that performances were adversely affected, without specifying the parameter that was affected. Therefore, the present review indicates only that some aspect of the performance was affected by the drug.

1. Effects in normal subjects. Results of studies com-

paring effects of acute doses at therapeutic levels are shown in table 2. These studies examined the effects of doses within the therapeutic range, either administered once to each subject or repeated with sufficient time between doses that tolerance was unlikely to have developed. An entry was made in the tables for each dose compared to predrug value or placebo value. The table shows ratios of the number of doses producing performance decrements to the number of dose comparisons made.

An examination of the rows that sum all of the effects across test procedures indicates that psychomotor performances were affected more often when effects were assessed immediately after drug administration than when assessed the next morning after bedtime administration. Across experimental procedures, some drugs produced effects more consistently than others. For example, flurazepam was very likely to have effects on performances immediately after administration, whereas alprazolam and chlordiazepoxide were less likely to produce such immediate effects. However, there was a considerable amount of variability across studies, since no drug under any procedure consistently produced either some effect or no effect.

The most information for a single drug was available for diazepam. Of the effects of diazepam, the highest ratios of effects were observed with critical flicker fusion frequency (CFF) and choice reaction time. Also affected frequently were tracking, digit-symbol substitution test (DSST), reaction time, and cancellation. Affected least frequently were arithmetic, sorting tasks, and divided attention tasks. In studies in which diazepam was given i.v., effects were obtained frequently in most of the tasks; the exceptions were choice reaction time and divided attention.

Ghoneim et al. (354) directly compared the effects of

TABLE 2

Effects of therapeutic doses on psychomotor performance in normal subjects. References are given in appendix 1.

Drug	Route	CFF*	TAPP†	DSST‡	TRAC§	RT‖	CRT¶	CANC#	ARITH**	SORT††	DV ATT‡‡	Totals§§
Alprazolam	p.o.	1/2		1/2	1/2	0/1	0/2	0/1				0.30 (10)
Chlordiazepoxide	p.o.	1/3			0/6	1/2	4/5		1/1			0.41 (17)
Clorazepate	p.o.	2/5	2/3	2/3		0/4	0/1	0/3	0/1			0.30 (20)
Diazepam	p.o.	20/24	5/13	10/15	12/29	8/17	12/18	7/12	1/5	0/3	3/10	0.53 (146)
Diazepam	i.v.	6/7	4/4	4/4	6/7	4/6	3/8	3/3	5/5		1/5	0.73 (49)
Flurazepam	p.o.	1/1		4/4	2/2	0/1	0/2	0/1	2/2	2/2	2/2	0.76 (17)
Flunitrazepam	p.o.				1/1							1.00 (1)
Lorazepam	p.o.	12/15		6/7	7/9	8/14	4/4	5/5	0/2			0.75 (56)
Nitrazepam	p.o.	2/3		4/9	1/1	2/3	1/1			4/4		0.67 (21)
Oxazepam	p.o.	4/5			4/4	1/4	0/3				0/2	0.50 (18)
Temazepam	p.o.			2/2	3/5	0/1	2/5	1/2	1/2			0.53 (17)
Triazolam	p.o.	0/1		2/6	0/1	1/1	0/1	1/2		3/3		0.47 (15)
Totals§§	p.o.	0.73 (59)	0.44 (16)	0.65 (48)	0.52 (60)	0.44 (48)	0.55 (42)	0.54 (26)	0.38 (13)	0.75 (12)	0.36 (14)	0.56 (338)
Chlordiazepoxide	p.o., h.s.‖‖			1/1								1.00 (1)
Diazepam	p.o., h.s.				1/5							0.20 (5)
Flurazepam	p.o., h.s.		0/3	4/9	4/6	0/3	2/6	0/3	3/4	2/4		0.39 (38)
Flunitrazepam	p.o., h.s.		1/1	2/4	1/5	0/1		0/1		0/1		0.31 (13)
Nitrazepam	p.o., h.s.	2/7	3/9	4/8	1/2	4/13	3/11	2/3	0/2	3/4		0.37 (59)
Oxazepam	p.o., h.s.				1/3	0/1					0/1	0.20 (5)
Temazepam	p.o., h.s.	3/10		2/3	0/6	0/5	3/10	0/2	1/2	0/2		0.23 (40)
Triazolam	p.o., h.s.	0/1	0/1	4/7	1/5		0/1	0/2		1/1		0.33 (18)
Totals§§	p.o., h.s.	0.28 (18)	0.29 (14)	0.53 (32)	0.28 (32)	0.17 (23)	0.29 (28)	0.18 (11)	0.50 (8)	0.50 (12)	0.00 (1)	0.33 (179)

* CCF, critical flicker fusion frequency (the threshold frequency at which flickering light appears steady).

† TAPP, tapping (the maximal rate at which the subject can tap his finger).

‡ DSST, digit symbol substitution test (subjects are presented with a code in which the numbers 1 to 9 are matched with simple symbols. For a fixed time period, they write the appropriate symbols below a series of numbers).

§ TRAC, tracking (subjects indirectly manipulate an object through the use of some type of manipulandum to keep it on target).

‖ RT, reaction time (the subject is required to respond to a stimulus by pressing some type of key as fast as possible).

¶ CRT, choice reaction time (subjects are required to respond differentially, and as fast as possible, to two stimuli that are presented in random order).

CANC, cancellation (subjects are required to strike through particular letters on a printed page).

** ARITH, arithmetic (subjects are required to perform sequential arithmetic problems without benefit of paper and pencil).

†† SORT, sorting (subjects are required to sort objects according to some rule; e.g., a deck of playing cards are sorted by suit.

‡‡ DV ATT, divided attention (subjects are required to monitor at least two stimuli which cannot be focused on simultaneously and to respond to the stimuli in different ways).

§§ Totals give proportions of dose comparisons showing effects, followed by the number of dose comparisons in parenthesis. The totals for columns exclude intravenously administered diazepam.

‖‖ h.s., administered at bedtime.

diazepam administered orally and intravenously. As expected, onset of action was faster when the drug was administered intravenously. Additionally, greater maximal effects were obtained on tapping performances when the drug was administered intravenously. The rate of recovery of performances also depended on the route of administration; the rate of recovery was more rapid when diazepam was administered intravenously. The differences in effects obtained with intravenous and oral administration may be due to differences in rates of absorption (cf. ref. 88). Thus, the present comparisons regarding a given drug across studies using different routes of administration may be influenced by the time after dosing when the effects were examined, so that such comparisons may be of limited value. However, it does appear that effects were obtained more often when diazepam was administered intravenously than when it was administered orally.

The performances generally most sensitive to the immediate effects of the benzodiazepines, on the basis of the frequencies of reported effects across drugs at therapeutic doses, were CFF, DSST, and sorting. The test performances that were generally least sensitive were arithmetic and divided attention. Several deviations from these generalizations deserve comment. Although tracking performance was affected relatively frequently by therapeutic doses of flurazepam, lorazepam, oxazepam, and temazepam, it was generally not affected by therapeutic doses of chlordiazepoxide and was affected relatively infrequently by diazepam. Lorazepam generally affected DSST, tracking, choice reaction times, and cancellation with a greater frequency than did the other drugs. Certain drugs also appeared more likely to have effects than others. Flurazepam, lorazepam, and, to a lesser extent, nitrazepam produced effects on the various psychomotor performance tests with a frequency similar to that for intravenously administered diazepam.

In general, when subjects were tested in the morning after bedtime drug administration, effects were found less frequently than when testing was performed soon after administration. For example, diazepam affected tracking performances in 1 of 5 comparisons of therapeutic doses given at bedtime, whereas it affected 12 of 28 therapeutic dose comparisons when subjects were tested relatively soon after the drug was administered; similarly, nitrazepam and flunitrazepam affected far fewer performances when tested the morning after bedtime administration than when subjects were tested soon after administration. Likewise, most types of psychomotor tests showed effects less frequently the morning after bedtime administration than when they were performed soon after drug administration; those most often affected when performed on mornings after bedtime administration were DSST, arithmetic, and sorting. Thus, observations of the effects of the benzodiazepines on performance measures apparently depend to some extent on the time when these effects are tested. However, it is unclear whether the differences are due simply to the time elapsed since drug administration, or whether intervening sleep may have an independent effect on performances the morning after drug ingestion.

Examination of table 2 reveals differences among drugs on each type of performance test, as well as differences among effects of each drug on different types of performances. The differences among drugs, with regard to which performances were most often affected by each drug, suggest differences in the behavioral effects of the different benzodiazepines; however, the differences noted in one study may be contradicted by results in another study.

Few studies have examined the effects of doses above the therapeutic range. Studies that have examined performances immediately after administration of high doses (table 3) have generally found effects of the drugs

TABLE 3

Effects of high doses on psychomotor performance in normal subjects

Study	Drug	Dose (mg)	CFF*	TAPP	DSST	TRAC	RT	CRT	CANC	ARITH	SORT	DV ATT
659	Flunitrazepam	2.0				D†						
789	Flurazepam	50.0										D
407	Nitrazepam	15.0	D									
876	Temazepam	40.0			D	D			D			
996	Flunitrazepam	2.0 (h.s.)‡	D			D		NE				
659	Flunitrazepam	2.0 (h.s.)				NE	NE					NE
114	Flunitrazepam	2.0 (h.s.)		D	NE		NE		NE		D	
1140	Flunitrazepam	2.0 (h.s.)							NE			
728	Flunitrazepam	2.0 (h.s.)							D			
478	Temazepam	40.0 (h.s.)	NE					NE		NE	NE	
434	Temazepam	40.0 (h.s.)					NE		NE			
434	Temazepam	50.0 (h.s.)					NE		NE			
434	Temazepam	60.0 (h.s.)					NE		NE			
478	Temazepam	60.0 (h.s.)	NE					NE		NE	NE	
1112	Triazolam	1.0 (h.s.)			D						D	

* Refer to footnotes to table 2 for a description of psychomotor tests and abbreviations.

† D, decrement in some aspect of performance; NE, no effect.

‡ h.s., administered at bedtime.

studied, except that no effect of temazepam was observed on arithmetic testing. When the drugs were administered at bedtime and performances tested on the following morning, fewer dose comparisons showed effects. Although there were far fewer studies at doses above the therapeutic range, the proportions of dose comparisons that showed effects in these studies were not appreciably different from the proportions of studies that showed effects at doses within the therapeutic range.

Since benzodiazepines are generally prescribed for treatment periods of at least several days, assessments of the effects of these drugs on performance should also examine the effects of these drugs over testing periods of comparable length. These studies should be able to assess the additive effects of successive doses or the tolerance that can develop with repeated doses. Table 4 is a summary of reported effects of several benzodiazepines on performance during regimens of at least 6 days of repeated dosing. The table lists the total dose administered per day as well as how the drug was given (i.e., how many times per day and if the drug was given at bedtime).

Of the individual benzodiazepines, diazepam appears to have been studied on the greatest number of performance tests. No effects were generally observed on CFF, tapping, DSST, choice reaction time, and arithmetic. Occasional effects on tracking and divided attention have been reported; these effects occurred at doses of either 15 or 30 mg per day. All of the effects on performance reported with diazepam were for doses within the therapeutic range.

Another drug frequently studied after 6 or more days of repeated dosing is flurazepam. One study examined the effects of 15 mg per day and found no effects on any

TABLE 4

Effects of repeated doses on psychomotor performance in normal subjects

Study	Drug	Mg/day (how delivered)	CFF*	TAPP	DSST	TRAC	RT	CRT	CANC	ARITH	SORT	DV ATT
24	Alprazolam	0.75 (t.i.d.)†	NE‡‡		NE	NE		NE				
1060	Alprazolam	1.5 (t.i.d.)	NE			NE		NE				NE
952	Chlordiazepoxide	30.0 (t.i.d.)	NE			NE		NE				NE
667	Chlordiazepoxide	30.0 (t.i.d.)				NE		NE				NE
664	Chlordiazepoxide	30.0 (t.i.d.)										
620	Clorazepate	7.5, 15.0 (q.d.)	NE	NE	NE		NE		NE			
843	Diazepam	6.0 (t.i.d.)	NE			NE						NE
369	Diazepam	10.0 (q.d.)		NE								
645	Diazepam	10.0 (q.d.)	NE			D						
353	Diazepam	15.0 (q.d.)		NE						NE		
470	Diazepam	15.0 (t.i.d.)	NE									
24	Diazepam	15.0 (t.i.d.)	NE		NE	NE		NE				
642	Diazepam	15.0 (t.i.d.)								NE		
952	Diazepam	15.0 (t.i.d.)										NE
666	Diazepam	15.0 (t.i.d.)				D						NE
664	Diazepam	15.0 (t.i.d.)				NE						NE
790	Diazepam	15.0 (t.i.d.)										D
843	Diazepam	30.0 (t.i.d.)	NE			D						D
959	Flurazepam	15.0 (h.s.)		NE		NE	NE					
959	Flurazepam	30.0 (h.s.)		D		D	NE					
760	Flurazepam	30.0 (h.s.)		D					NE			
122	Flurazepam	30.0 (h.s.)		NE	NE			NE				
834	Flurazepam	30.0 (h.s.)			D						D	
123	Flurazepam	30.0 (h.s.)			D							
952	Flurazepam	30.0 (h.s.)				D		NE				NE
953	Flurazepam	30.0 (h.s.)				D		NE				NE
169	Flurazepam	30.0 (h.s.)						D				
1060	Lorazepam	6.0 (t.i.d.)	NE			D		D				
960	Nitrazepam	5.0 (h.s.)		NE	NE							
1077	Nitrazepam	10.0 (h.s.)	NE					D				
722	Nitrazepam	10.0 (h.s.)	NE		NE	NE		NE				
952	Nitrazepam	10.0 (h.s.)	NE			D		NE				
954	Nitrazepam	10.0 (h.s.)						NE				
840	Oxazepam	45.0 (t.i.d.)	NE			NE		NE				NE
234	Oxazepam	30.0 (t.i.d.)	D									
722	Temazepam	20.0 (h.s.)	NE		NE	NE		NE				
1077	Temazepam	20.0 (h.s.)	NE					D				
122	Triazolam	0.5 (h.s.)		NE	NE			NE				

*Refer to footnotes to table 2 for descriptions of abbreviations.

† t.i.d., 3 times a day; q.d., every day; h.s., bedtime.

‡‡ NE, no effect; D, decrement in psychomotor performance.

of the performances studied. Following 30 mg administered on the previous night, effects were uniformly reported on tracking and, in one study, on sorting performances. Effects were obtained in some studies on tapping, DSST, and choice reaction times. In the one study that examined reaction times, no effects were observed.

Other drugs reported to affect some performance measures after 6 or more days of repeated administration were lorazepam, nitrazepam, oxazepam, and temazepam. Each of these drugs had an occasional effect on either tracking or choice reaction time, with the exception of oxazepam, which affected CFF.

All of the tests employed with some frequency showed occasional effects of some of the drugs. In general, however, repeated doses produced few effects. Comparison of these findings with the effects observed after single doses suggests that a considerable degree of tolerance to these effects on performance develops within a few days of repeated dosing with benzodiazepines.

2. Effects in anxious subjects. Since benzodiazepines are most frequently prescribed for individuals suffering from anxiety or insomnia, it is of interest to determine the effects of these drugs in these specific populations. Table 5 shows results of studies conducted in anxious subjects. In most of these studies, subjects were diagnosed as suffering from anxiety; however, in some studies (235, 234, 470), subjects were regarded as anxious on the basis of their scores on scales of anxiety. Studies that experimentally induced anxiety or stress in normal subjects were not included.

Only a few studies examined the effects of single doses on performance, and most of these studies examined effects of diazepam at therapeutic doses. Decreases in CFF threshold and in the number of correct responses or latencies in choice-reaction-time procedures were obtained in all of the studies that examined these effects. No effects of diazepam were observed on tasks involving divided attention. With respect to tracking and vigilance performances, some studies have found performance decrements and others have not. In one study (470), which examined a single, 20-mg dose of clobazam administered at bedtime, the effects on a choice-reaction-time task the next morning were found to vary with the subjects' scores on the Eysenck Personality Inventory (280); performance was impaired in subjects with relatively high or relatively low scores, whereas performance was improved in subjects with intermediate scores. Taken together, the results of studies of single doses in anxious patients (table 5) were not appreciably different from results of studies in normal subjects (table 2).

In most studies of anxious subjects, the drugs were given repeatedly at therapeutic doses over several days, as they would be administered therapeutically. The largest number of studies examined the effects of diazepam, and the results have varied among studies. At least one study found decreases in all of the performance measures taken, except vigilance and mental arithmetic (table 5). Decreases in tracking-performance accuracy have been reported with some reliability; decreases were obtained in five of six studies using this procedure. Although there was also some variation in findings among studies in normal subjects (table 4), at least with some procedures these findings appeared more consistent than those obtained in studies of anxious subjects. The differences between studies examining normal and anxious subjects may have been due to differences in the doses used and in the durations of treatment.

Of the other drugs whose effects were studied after repeated administration to anxious subjects, only flurazepam, oxazepam, and clobazam have been reported to have any effects on psychomotor performances. However, only a few studies of these drugs have been reported (table 5).

A few studies have directly compared effects of benzodiazepines on performances of normal and anxious patients. Linnoila et al. (660) examined the effects of diazepam at doses of 5 and 10 mg. Normal subjects showed decreases in tracking performance and in correct responses in a task involving concurrent visual search and tracking. Anxious subjects also showed decrements in these performances, but only after 1 wk of repeated administration of three doses per day; the normal subjects were tested only after a single dose. Diazepam had no effect on other performances in either normal or anxious subjects. In another study (234), the rate of tapping was decreased by oxazepam in anxious subjects but not in normal subjects; tracking performance was not affected in either type of subject.

A study of a group of long-term users of a variety of benzodiazepines (863) found impaired performance on symbol copying and DSST tests, as compared to performances of a group of normal control subjects that had not received drugs. The authors concluded that tolerance did not develop to the effects of benzodiazepines on these performances. However, other studies (681, 679, 680) compared groups of long-term users of various benzodiazepines with age- and sex-matched anxious control subjects; results of these studies suggested that tolerance did develop to the effects of the drugs on symbol copying and DSST performances. The discrepancies between the results of these studies and that reported by Petursson et al. (863) appear to be due to the differences in the control groups that were used, namely that Petursson and coworkers compared anxious and normal subjects.

Indeed, Bond et al. (110) had previously demonstrated that, without drug administration, anxious subjects do not perform as well as normal subjects on several tests including symbol copying and DSST. Thus, to assess whether tolerance has developed to drug effects in anxious subjects, their performances following drug administration should be compared with their own performances prior to drug administration, or to performances of nondrugged anxious subjects, rather than to performances of normal subjects. A given drug may have different

TABLE 5

Effects on psychomotor performance in anxious subjects

Study	Drug, dose(s) in mg	STEAD*	CFF†	TAPP	DSST	TRAC	RT	CRT	CANC	ARITH	SORT	DV ATT	VIG‡	CID§
Single doses														
955	Diazepam, 5 or 10		D‖			NE		D				NE		
952	Diazepam, 5–10		D			D		D				NE		
661	Diazepam, 10					D		D					D	
660	Diazepam, 5, 10					NE						NE	NE	
470	Clobazam, 20							I						
Repeated doses														
235	Chlordiazepoxide, 15			NE		NE				NE				
111	Chlordiazepoxide, 28			NE	NE		NE		NE	NE	NE			
873	Chlordiazepoxide, 30													NE
818	Clobazam, 20		NE		NE			NE						
471	Clobazam, 30 (5 days only)													
242	Clobazam, 30–40	D (I)¶												
958	Clobazam, 35				NE	D								
111	Diazepam, 11			NE	NE		NE		NE	NE	NE			
958	Diazepam, 17				D	D								
660	Diazepam, 15					NE						NE††	NE	
660	Diazepam, 30					D						D††	NE	
955	Diazepam, 15–30		D (day 7), NE (day 14)				D		D				NE#	
242	Diazepam, 15–20	D												
952	Diazepam, 15–30		D			NE		NE				NE		
1075	Diazepam,‡‡ ~25			D	NE				D	NE	D			
661	Diazepam, 30					D		NE				NE		
340	Flurazepam, 30 (h.s.)**						D							
818	Lorazepam, 2		NE		NE			NE						
111	Medazepam, ~27			NE	NE		NE		NE	NE	NE			
702	Nitrazepam,‡‡ 5, 10 (h.s.)				NE						NE			
234	Oxazepam, 30			D§§		NE								
340	Triazolam, 0.5 (h.s.)						NE							

* STEAD, steadiness (hand steadiness).
† Refer to footnotes in table 2 for a description of most abbreviations; others are below.
‡ VIG, vigilance (detection of an infrequently presented visual stimulus on a cathode ray tube).
§ CID, concept identification (assigning category rules to groups of stimuli).
‖ D, decrement in performance; NE, no effect; I, improvement in performance.
¶ Improvement for subjects with high degree of unsteadiness.
# Decrease in some aspect of performance on day 7 but not day 14.
** h.s., bedtime.
†† Two tests, one with and one without a "visual search" component. The one with a "visual search" component was affected.
‡‡ Subjects were also insomniacs.
§§ No effect on normals.

effects on the performance of normal and anxious subjects, but it should be noted that baseline differences in these populations (110) may increase the likelihood of performance differences following drug administration.

3. Effects in insomniac subjects. Effects of benzodiazepines on psychomotor performance in subjects suffering from insomnia are shown in table 6. Subjects in these studies were selected on the basis of either subjective or objective measures indicating poor quality or duration of sleep. In some of the studies, subjects were also suffering from anxiety (1075, 702) or were also elderly (157, 117, 668). Most of the studies examined residual effects in the morning after administration of drugs at night. The drugs studied most often were, as one might expect, drugs prescribed for nighttime sedation.

Only a few studies examined the effects of single doses on performances, and all of these studies examined effects in the morning following bedtime administration. Nitrazepam (853) had no effects on tapping rate, DSST, or reaction times at doses of 2.5 and 5 mg. The number of signals detected in an auditory vigilance task was not affected at 2.5 mg and was increased at 5 mg. All of the performances studied were adversely affected by 10 mg of nitrazepam. Similarly, temazepam (472) did not alter choice reaction time at a relatively high dose (30 mg). Midazolam given at bedtime on two successive evenings (442) did not affect balance at any dose, nor DSST or pegboard performances at doses of 5 and 10 mg. A higher dose, of 20 mg, decreased performance on the DSST and pegboard tests.

In most studies of subjects suffering from insomnia, the drug was given repeatedly at therapeutic doses over several days, as it would be administered therapeutically. Table 6 also shows studies examining the repeated effects of the drugs; unless otherwise specified (by parenthetical numbers following entries), these studies examined effects after at least 6 days of drug administration. Three studies each examined the effects of nitrazepam and triazolam. Across most of the measures of performance studied, 5 and 10 mg of nitrazepam had no effects (table 6), and a decrease in the rate of tapping was found after 10 mg in a group of elderly subjects. Triazolam, at doses

TABLE 6

Effects on psychomotor performance in insomniac subjects

Study	Drug, dose(s) in mg	BAL*	TAPP†	DSST	TRAC	RT	CRT	CANC	ARITH	SORT	VIG	DEXT‡
Single doses												
442	Midazolam, 5, 10, 20 (h.s.)§	NE‖		NE (5, 10) D (20)								NE (5, 10) D (20)
853¶	Nitrazepam, 2.5, 5, 10 (h.s.)		NE (2.5, 5) D (10)	NE (2.5, 5) D (10)		NE (2.5, 5) D (10)				NE (2.5)	I (5), D (10)	
472	Temazepam, 15, 30 (h.s.)						NE (15) D (30)					
Repeated doses												
609	Alprazolam, 0.5 (h.s.)	NE		NE						NE		NE
1075#	Diazepam, 25		D	NE		NE	NE	D	NE	D		
658	Flunitrazepam, 2 (h.s.)				NE	NE					NE	
157**	Flurazepam, 15 (h.s.)			D (day 3)						D (day 3)	D (day 3)	
662	Flurazepam, 30 (h.s.)				NE	NE					NE	
117**	Ketazolam, 30 (h.s.)	D										
960	Loprazolam, 1 (h.s.)		NE	NE	NE							
1126**	Lorazepam, 3 (h.s.)			D						D		
960	Nitrazepam, 5 (h.s.)		NE	NE	NE							
702#	Nitrazepam, 5, 10 (h.s.)			NE						NE		
668**	Nitrazepam, 10 (h.s.)		D									
928	Temazepam, 30 (h.s.)			NE								
157**	Triazolam, 0.25 (h.s.)			D (day 3)						D (day 3)	NE	
1121	Triazolam, 0.25, 0.5, 1.0 (h.s.)		NE							NE		
1031	Triazolam, 0.5 (tested immediately or after sleep)			D, NE (h.s.)			D, NE (h.s.)				D, NE (h.s.)	

* BAL, balance (subject asked to stand on an unstable platform).
† Refer to footnotes in tables 2 and 5 for descriptions of most abbreviations; others are below.
‡ DEXT, dexterity (fitting pegs into appropriate holes).
§ h.s., bedtime.
‖ NE, no effect; D, decrement in performance; I, improvement in performance.
¶ Subjects also anxious.
# Compared to normal subjects.
** Subjects also elderly.

of 0.25 to 1.0 mg, also had no effects the morning after bedtime administration (1121, 1031); however, if subjects were awakened a few hours after administration of 0.5 mg, performances were found to be decreased (1031). Triazolam also had effects at 0.25 mg on the third day of administration to elderly subjects suffering from insomnia (157). Flurazepam at 15 mg also decreased several performance measures after 3 days of administration to elderly subjects (157); however, twice this dose had no effects on younger subjects suffering from insomnia (662).

Of the other drugs studied after repeated administration to subjects suffering from insomnia, only diazepam (1075) and lorazepam (1126) have been reported to have any effects on psychomotor performances. These drugs have been examined in only a few studies (table 6); however, the results are generally consistent with results obtained in studies of normal subjects (table 2). These results are as expected, since the drugs were given at bedtime, and effects of the drugs were assessed the next morning, when much of the effect should have diminished, and since the drugs were given repeatedly, allowing the development of tolerance.

One study has directly compared effects of single doses of nitrazepam on performances of normals and subjects suffering from insomnia. Peck et al. (853) compared effects of single doses in groups of sound and light sleepers that were also matched for age. Effects on tapping rate and DSST were not different in the two groups of subjects; decreases in performance were obtained at doses of 10 mg, with no effects at lower doses. Reaction times were decreased in normal subjects at 5 mg, but were affected in light sleepers only at a dose of 10 mg. In the light sleepers, auditory vigilance was not affected by 2.5 mg, improved at 5 mg, and decreased at 10 mg. Sound sleepers showed no effects of any of these doses on their auditory vigilance performance. Thus, this study found significant improvements, only in insomniac subjects, in some, but not all, performances on the morning after nitrazepam administration; and it found decrements in some, but not all, performances in normals at a dose that did not alter the performance of insomniacs. As in studies comparing anxious and normal subjects, insomniac and normal subjects showed baseline differences on some behavioral measures; however, these differences were not evident in all tests in which the groups differed with respect to drug effects.

4. Effects in elderly subjects. Studies of the epidemiology of benzodiazepine use indicate that the elderly take proportionately more of these drugs than does the population under 50. Older people are also more likely to take benzodiazepines chronically, and they are more likely to take them in conjunction with other medications (see section V F 1, pages 367 to 370). Evidence also strongly suggests that the elderly are more sensitive to the effects of benzodiazepines than are younger people. Three studies of the Boston Collaborative Drug Surveillance Program indicated that benzodiazepines produce more sedation and unwanted depression in older hospitalized patients than in younger hospitalized patients (20, 381, 379).

Several studies have examined the effects of benzodiazepines on the performance of elderly subjects. Single doses of diazepam as low as 2.5 to 10 mg slowed choice reaction times in older subjects (878) and disrupted several types of memory tasks, but did not alter CFF thresholds (880). Nitrazepam (5 mg) given at bedtime to elderly inpatients did not impair choice reaction times or performance on a cancellation task the following morning (191). Temazepam (20 mg) was reported in one study not to affect performance on a cancellation task in elderly, confused patients (749), and in another study to adversely affect performance on a cancellation task in elderly inpatients (191).

In most studies of elderly subjects, the tested benzodiazepine was given repeatedly at therapeutic doses over several days, as it would be administered therapeutically. Decreases in performance measures have been obtained with most drugs for all of the procedures studied (table 7). The exception was alprazolam, for which no effects were observed the morning after a nighttime dose of 0.5 mg. There were some indications of tolerance to some of the effects of diazepam (5 mg) and halazepam (20 and 40 mg) given 2 or 3 times daily (327). Effects were greater after the 3rd than after the 14th night. On the other hand, an increase in drug effects was observed with 7 days of daily administration of nitrazepam (5 mg) or temazepam (20 mg) (191). A further slowing of choice reaction time and letter cancellation was observed on the seventh morning of drug administration.

The information on the effects of benzodiazepines on older subjects is not particularly useful unless comparisons are made with younger subjects. The results displayed in table 7 suggest that more consistent decrements in performances were obtained in elderly subjects than in younger subjects (table 4). Better evidence to support this suggestion has been obtained in studies that compare older and younger subjects directly. Since direct comparisons of this kind are rare, we review here some comparisons in studies whose end points are not typically categorized under psychomotor performance.

Giles et al. (358) administered diazepam intravenously to 19 patients in preparation for endoscopy. The end point of drug administration was sufficient relaxation to permit endoscopic intubation. The dose of diazepam required to produce sufficient sedation was negatively correlated with age, indicating that the older patients were more sensitive and required less drug than the younger patients to produce the same degree of relaxation. The correlation between blood levels and administered dose was high and positive for the population as a whole; the differences in sensitivity were therefore not due to equally high blood levels resulting from administration of different doses.

TABLE 7

Effects on psychomotor performance in elderly subjects

Study	Drug, dose(s) in mg	BAL*	CFF†	DEXT	DSST	CRT	CANC	SORT	VIG	TAPP
Study doses										
878	Diazepam,† 2.5		NE‡			D				
880	Diazepam, 2.5, 5.0, 10.0		NE			D				
191	Nitrazepam, 5.0 (h.s.)					NE	NE			
749	Temazepam, 20.0 (h.s.)						NE			
191	Temazepam, 20.0 (h.s.)					NE	D			
Repeated doses										
609	Alprazolam,§ 0.5 (h.s.)	NE			NE			NE		
327	Diazepam, 15–10		D (day 3), NE (day 14)							D (day 3, 14)
157	Flurazepam,§ 15 (h.s.)				D (day 3)			D (day 3)	D (day 3)	
327	Halazepam, 60–40		D (day 3), NE (day 14)							D (day 13, 14)
327	Halazepam, 120–80		D (day 3, 14)							D (day 3–14)
117	Ketazolam,†,§ 30 (h.s.)	D								
191	Nitrazepam, 5 (h.s.)					D	D			
783	Nitrazepam, 5 (h.s.)			D						
668	Nitrazepam,§ 10 (h.s.)			D						
191	Temazepam, 20 (h.s.)						NE			
157	Triazolam,§ 0.25 (h.s.)				D	D		D	NE	

* Refer to footnotes in tables 2, 5, and 6 for descriptions of abbreviations.

† Compared to young subjects.

‡ NE, no effect; D, decrement in performance.

§ Subjects also insomniacs.

In a similar study, Reidenberg et al. (911) determined the amount of i.v. diazepam necessary for cardioversion in 23 subjects. The end point occurred when the patient did not respond to a verbal stimulus, yet withdrew from a painful stimulus. As might be expected from patients requiring cardioversion, most of these subjects were older; although the correlation was calculated across the entire age range, from 30 to 90 yr, only 2 of the 23 subjects were less than 53 yr of age. These investigators reported, as had Giles et al., a very high positive correlation between dose administered and plasma level of diazepam. They also reported a significant negative correlation between age and required dose and between age and plasma level resulting from administered dose. The authors concluded that elderly patients required lower doses of diazepam than did younger patients to produce the same level of CNS depression, and that this difference was due to pharmacodynamic alteration in the response to the drug.

Castelden et al. (158) evaluated the sensitivity of two groups each of 10 healthy subjects to nitrazepam in a double-blind, placebo-controlled study. In one group, the subjects were all over 69 yr of age (mean, 74.7 yr), whereas the subjects in the other group were all less than 40 yr of age (mean, 25.3 yr). The subjects were asked to take a single dose of nitrazepam (10 mg) or placebo, apparently at bedtime. Plasma samples were drawn for analysis of nitrazepam at 12, 36, and 60 h after tablet administration. At the same time, a cancellation test was given to measure psychomotor performance, and the subjects were asked to indicate how well they had slept the previous night and how awake they felt at the present time. The data indicated no difference between plasma nitrazepam levels in the young and elderly groups. The half-lives and apparent volumes of distribution were likewise not different between these groups. The elderly made more mistakes than the young following placebo administration, indicating an already impaired ability to perform this task. There was no significant difference in the number of errors made by the young group following placebo or nitrazepam administration at 12 and 36 h. The elderly made significantly more mistakes at 12 and 36 h following nitrazepam administration than they had following placebo. They were also much slower than the younger subjects in the absence of any drug, and both groups took significantly longer to complete the test at 12 and 36 h following drug administration. The marked differences in the two groups in rate and accuracy in the test in the absence of drug administration emphasize the need for careful measures of subjects' baseline conditions.

Crooks (210) reported the effects of temazepam (20 mg) on groups of nine young (20 to 27 yr) and nine older (68 to 79 yr) subjects. Measures included body sway, CFF, choice reaction time, and subjective ratings of sedation. The older subjects had higher baseline values for both body sway and choice reaction time than did the young. Temazepam produced a more rapid and prolonged increase in body sway and CFF in the older subjects. Body sway was also increased considerably more in the

older subjects, whereas both measures were affected by temazepam in the elderly. Although temazepam had a short half-life and an "uncomplicated" elimination pathway, the plasma concentrations of temazepam remained elevated longer in older subjects. However, up until 6 h after administration, the time of the last test, plasma levels of the benzodiazepine were the same in both groups. Crooks concluded that pharmacokinetic data were not sufficient to predict clinical usefulness of benzodiazepines.

Pomara et al. (878) examined the effects of a single 2.5-mg dose of diazepam in young (mean age, 25.9 yr) and elderly (mean age, 70.4 yr) subjects and found decreases in choice reaction time performance in elderly but not young subjects. No effects were obtained on CFF thresholds in either group of subjects. The elderly subjects showed higher plasma concentrations of diazepam than the young subjects. Bonnet and Kramer (117) measured performance on a balance board in young and elderly insomniacs. The older subjects spent twice as much time off balance than did the younger subjects under baseline conditions. With repeated daily administration of 30 mg of ketazolam, elderly subjects (mean age, 66 yr) exhibited increased impairment of balance over the course of a 7-day treatment period, whereas young subjects (mean age, 23 yr) improved.

It is clear from these studies that older people may be more affected by the same dose of benzodiazepines or may require less of the drug to obtain the same effect than younger people. The reason for this difference is not at all clear. There are a large number of studies comparing the capacities of younger and older people to metabolize benzodiazepines. The data are frequently in conflict, both as to whether older people metabolize benzodiazepines more slowly, and whether "appropriate" measures of benzodiazepine levels in the blood have been taken. There is a fairly general consensus that older people are less different from younger people in their capacity to metabolize benzodiazepines with short half-lives, i.e., those that are metabolized through conjugation rather than by N-demethylation (e.g., refs. 383, 381, and 965), and a preference for those benzodiazepines on the part of physicians prescribing for older people is often recommended.

Investigators frequently call on pharmacodynamic rather than pharmacokinetic factors to explain differential responses by older people to benzodiazepines. Rarely is any attempt made to define the potential pharmacodynamic factors that may be involved. One point that seems clear from the literature but is not discussed in any detail by the investigators in this area is that older people are frequently different from younger people in the measures taken, even in the absence of drug. Thus, as Castelden et al. (158) and Crooks (210) demonstrated, older subjects were much more impaired and were slower in performing the required tasks than younger subjects, prior to drug administration. Older people often start from a different baseline in the psychomotor tests and may also start from a different baseline in evaluations of clinical response. The effects of benzodiazepines in some ways mimic the effects of old age; muscle strength and coordination are decreased, memory disturbances are increased, and confusion and disorientation are more likely when the conditions of benzodiazepine administration and old age are combined. As observed by Evans and Jarvis (278), benzodiazepine effects in older people resemble some forms of CNS disorders that can develop in this population. In a study of hospitalized patients over the age of 65, Cook et al. (191) found that impairment of psychomotor skills produced by temazepam or nitrazepam was not related to age, but was greater in patients with low intelligence. This is further evidence that baseline, predrug conditions may have a strong influence on the effects of benzodiazepines. It is possible that preexisting conditions of old age, although perhaps not always obvious, may be exacerbated by the administration of benzodiazepines.

5. Summary and discussion. As can any of the behaviorally active drugs, benzodiazepines can alter human psychomotor performance. Many studies indicate that the effects are obtained after single doses within the therapeutic range. When benzodiazepines are administered repeatedly, the effects diminish; after 6 days of treatment, there are far fewer effects than are observed after single doses. On the basis of the few studies that have been reported, it appears that the effects of the benzodiazepines on performance of anxious subjects do not differ from their effects in normal subjects.

As some previous reviews have found (e.g., ref. 741), there was no clear differentiation of the types of performances affected by the benzodiazepines. Other reviews (1163) have indicated that performances to which speed is essential may be affected more than other types of performance. There was no evidence of this differentiation of effects in the present review; for example, the single test in which effects were most often obtained was CFF, whereas the number of arithmetic problems completed was affected relatively infrequently.

Results reported for the benzodiazepines as a group were generally inconsistent, since performances on the different tests were often affected differently by different drugs. The fact that the studies reviewed did not differentiate the effects of benzodiazepines on different types of psychomotor performances suggests that either these drugs do not have specific effects on the different types of behaviors tested or the various tests do not isolate types of behaviors that differ in susceptibility to alteration by these drugs. The latter interpretation seems plausible, since the choice of particular tests appears to have been made on the basis of unsubstantiated intuitive assumptions that these tests are instruments that measure fundamental and distinct underlying processes.

It is not clear why the drug effects examined under these procedures appear so unreliable. Variations in en-

vironmental conditions among the studies presumably contributed to the differences in the effects observed. Another determinant of these discrepancies may have been a failure to account for differences in the subjects' baseline performances. A large number of studies of animal behavior have indicated that the effects of a single drug may differ dramatically depending on differences in baseline performances; for example, subjects that respond relatively infrequently are affected by drugs in a manner opposite to that of subjects that respond relatively frequently (233). In general, in contrast to the approach typically taken to assessing drug effects on human psychomotor performance, studies of behavioral pharmacology in animals have avoided presumptions regarding psychological processes that underlie behavior, by first establishing how a drug alters behavior and then examining the mechanisms involved through an experimental analysis (cf. ref. 233).

C. Effects on Recall

An amnestic effect of diazepam and its usefulness for patients prior to induction of surgical anesthesia was recognized fairly soon after its introduction. It appeared to produce amnesia for events surrounding the induction of anesthesia, as well as allaying the anxiety related to the surgical procedure (129, 441, 308, 913, 1063). There are some early, anecdotal reports of presurgical amnesia produced by benzodiazepines (881, 786, 253, 852, 139, 1054, 733), as well as reports of use of these drugs as anxiolytic and amnestic agents in dental surgery (570, 138, 237).

Since these early observations, there has been a substantial number of more rigorous studies designed to demonstrate the amnesia-inducing effects of the benzodiazepines. Methodologically, the studies fall fairly neatly into those studying patients prior to a surgical procedure and those studying healthy volunteers. There is also a more limited number of studies of benzodiazepine effects on recall of anxious subjects, elderly subjects, and subjects with insomnia.

The literature on the effects of benzodiazepines on recall has recently been reviewed by Lister (670), who considered this material in a manner similar to that of the present review.

1. Effects in patients prior to surgery. Studies in presurgical patients have usually looked simply for benzodiazepine-induced impairment of recall of procedures surrounding induction of anesthesia or of surgery itself. The investigators typically used a simple experimental design, often without double-blind, placebo controls, and the experimental definitions of amnesia were often imprecise. Interpretation of the results of these studies was complicated by the addition of the anesthetic agent, and frequently of other preanesthetic agents such as anticholinergics or narcotics. In some cases (e.g., ref. 268), the number of drugs used precluded any conclusions about the amnesia-inducing properties of the benzodiazepines. Despite such obvious drawbacks, studies of patients prior to surgery had the frequent advantage of using a large subject population. Moreover, this population was singularly representative of those most likely to receive benzodiazepines specifically for their amnesia-inducing properties.

In the least sophisticated procedures, patients were given a dose of a benzodiazepine at varying times before surgical anesthesia. Typically, 24 h later, following surgery, they were asked to recall general events that occurred between the time the benzodiazepine was administered and induction of anesthesia. Occasionally, a painful stimulus such as an abdominal pinch was applied, and recollection of this was tested later. In a frequently employed variation of this procedure, a specific stimulus or group of stimuli, usually on "memory cards," was shown to the subjects following administration of the benzodiazepine. Recall of the stimuli was usually tested 24 h following their presentation, and recognition was often tested as well by asking the subjects to select, from a group of similar cards, the cards they had been shown. The data were reported as the percentage of the subjects showing amnesia. In some studies, amnesia was indicated if the subject could not recall or recognize any of the stimuli; in other studies, amnesia was indicated if the subject failed to recall some of the stimuli.

By far the most typical routes of benzodiazepine administration to patients prior to surgery have been the oral, intramuscular, or i.v. routes. Two studies have used the rectal route of administration. In one, rectal administration of diazepam (0.6 mg/kg) to young children prior to dental treatment was shown to produce effective amnesia (303). In the other, rectal administration of diazepam at a mean dose of 30 mg was shown to produce a degree of amnesia for memory cards nearly equal to that produced by intravenous administration of diazepam at a mean dose of 13 mg, but with a slightly slower onset of action (686a).

a. ORAL ADMINISTRATION. Several investigators reported that orally administered diazepam (10 mg) produced little or no amnesia in presurgical patients (1157, 1058, 606). A dose of 20 mg was also relatively ineffective in producing amnesia (606). McKay and Dundee (735) studied the amnestic effects of orally administered diazepam (5, 10, or 20 mg), flunitrazepam (0.5 or 1 mg), and lorazepam (1, 2, or 4 mg). These doses approximate the therapeutic doses of each of these drugs. Amnesia was scored as complete, absent, or intermediate depending on the number of memory cards the patients could recall or recognize (none, all, or some, respectively). The percentage of patients showing intermediate or complete amnesia was noted for each drug condition. Each drug produced a dose-related amnesia. Five mg of diazepam were ineffective, whereas the 10- and 20-mg doses produced amnesia in 40 and 50% of the patients, respectively. The onsets of action of the two higher doses of diazepam were 20 to 30 min after drug administration;

the 20-mg dose produced a longer duration of amnesia. The time course of the effect of flunitrazepam was similar to that of 20 mg of diazepam (736). The highest dose of lorazepam was more effective, had a longer duration of action, and had a delayed onset, compared with the tested doses of diazepam or flunitrazepam.

The amnestic capacity of lorazepam had been noted by several other investigators (e.g., ref. 239). Lorazepam-induced amnesia was a function of the dose given (255, 606, 736), with maximal effects (70% or more of patients) occurring at doses of 4 mg (606, 736) or 8 mg (255). The amnestic effects of lorazepam (1 to 4 mg) appeared more profound in terms of the number of patients who showed reduced recall or recognition of stimuli, and they were of much longer duration than were those of diazepam (5 to 20 mg) (735, 606, 693, 1157, 145). The onset of amnesia occurred at about 1 h following lorazepam administration (128, 1058, 606); the peak effect appeared at about 2 h, and the duration was longer than 4 h (126, 597).

b. INTRAMUSCULAR ADMINISTRATION. Intramuscular administration of diazepam (10 mg) was also rather ineffective in producing amnesia (845, 145, 254). The largest effect was reported by Galloon et al. (330), who reported that 32% of patients could not recall at least one of three memory cards shown them approximately 90 min after they had received doses of diazepam that were given on the basis of body weight and ranged from 5 to 12.5 mg.

More patients failed to recall stimuli following administration of lorazepam [3 to 6 mg (330, 145) or 4 mg (312)] than following administration of diazepam [5 to 12.5 mg (330) or 10 mg (312, 145)]. Complete amnesia for events surrounding induction of anesthesia was produced in all patients by lorazepam [8 mg (255)], whereas lorazepam (4 mg) produced amnesia of either events surrounding surgery or of memory cards in from 48% to 68% of patients (255, 89, 462, 596). The duration of amnesia induced by lorazepam (4 mg or 0.03 mg/lb) was from 4 to 10 h (462, 201, 586).

Other investigators have reported less impressive degrees of amnesia following i.m. administration of lorazepam. A dose of lorazepam (0.06 mg/kg), given approximately 90 min prior to surgery, produced incomplete amnesia for events surrounding surgery. Only 34% of patients were amnestic for induction of nerve block anesthesia following this dose of lorazepam, and recollection of the surgical procedure itself was not impaired (598). There was no apparent relation between amnesia and plasma levels of lorazepam following administration of 0.03 or 0.06 mg/kg. These doses produced amnesia in slightly more than half of the individuals studied (605). Aleniewski et al. (8) found no significant failure of recall in patients who had received lorazepam (4 mg) 2 h prior to surgery.

Fragen et al. (313) demonstrated a profound amnestic effect in patients after i.m. administration of 0.08 mg/kg of midazolam. Over 87% of the patients failed to recall a memory card that had been shown to them 30 min after the injection.

c. INTRAVENOUS ADMINISTRATION. Diazepam appeared to produce amnesia in a larger proportion of patients if it was given by the i.v. rather than the i.m. route (254, 250). Profound amnesia has been demonstrated by several investigators who evaluated the effects of i.v. diazepam (doses were typically less than 20 mg) just prior to oral surgery (387, 44, 138, 237, 689, 826), forceps delivery (793), or cardioversion (548, 574). Doses of 5 (323), 10 (323, 189, 846), or 20 mg (846, 189) of diazepam were shown to produce a slight to moderate incidence of amnesia for stimuli presented 15 min after the injection.

It is possible that an increased incidence of amnesia might have been observed in these studies if the patients had been shown the stimuli sooner after drug administration. Much greater amnesia was observed when stimuli were presented immediately (603, 689) or 2 min (256), as compared to 14 to 30 min, after intravenous diazepam administration. Flinn et al. (305) observed that diazepam-induced amnesia lasted for only 24 min. Doses ranged between 0.125 mg/kg (603) and 17 mg (689), or until behavioral signs such as slurring of speech were observed (305). Gregg et al. (387) and Dundee and Pandit (256) found that both the incidence and duration of amnesia increased as a function of dose.

A much longer duration of amnesia was reported by Desjardins and Beaver (225), who found effects at 3 h following i.v. administration of up to 10 mg of diazepam, and at 4 h following i.v. administration of up to 30 mg of diazepam. The nature of the test was not described. Kortilla and Linnoila (600) found amnesia to abdominal pinch in volunteers who received 0.3 mg/kg or 0.45 mg/kg of diazepam 4 h earlier. A dose of 0.15 mg/kg was much less effective.

When delivered intravenously, flunitrazepam produced amnesia (601) that was of nearly the same degree as that produced by i.v. diazepam, but of slightly longer duration (250–252, 347). The number of patients showing amnesia following diazepam (10 mg) was similar to that found following flunitrazepam (1 mg) when both were given intravenously (347). Korttila et al. (603) noted a greater frequency of amnesia produced by flunitrazepam (0.01 mg/kg) than by diazepam (0.125 or 0.25 mg/kg).

Intravenous lorazepam has also been found to produce marked amnesia in presurgical patients (677). The effects were dose dependent, with 4 mg producing more and longer-lasting amnesia for memory cards than did 2 mg (839, 847). In some studies lorazepam produced amnesia in more patients than did diazepam (450, 827). The onset of amnestic action of intravenously delivered lorazepam was much slower than that of intravenously delivered diazepam or flunitrazepam, and the duration of action was much more prolonged (347), up to 270 min (251, 250). Doses of 4 mg produced a greater failure to recall than did doses of 2 mg (847, 839). Lorazepam (0.05 mg/

kg) did not produce amnesia in as many oral surgery patients as did diazepam (0.23 mg/kg) (44), perhaps because the surgery required less than 5 min and the medication was given only 5 min before administration of the local anesthetic. Four mg of lorazepam in combination with meperidine produced a greater and longer-lasting amnesia than meperidine alone (1076).

The most rapid onset and shortest duration of amnesia were produced by i.v. administration of midazolam. Five mg of midazolam produced a "transient but consistent" amnesia that was maximal at 2 to 5 min after administration and had disappeared within 30 min (259). An i.v. dose of 0.125 mg/kg of midazolam produced some impairment of recall in patients, but had a long recovery period relative to thiopental (95).

The question of whether amnesia developed in the absence of strong sedative effects has usually been examined in a fairly casual way, if at all, in these studies. Apparently strong sedative effects accompanied the amnesia-inducing effects of the benzodiazepines regardless of route of administration (e.g., ref. 128), but the patients were almost always awakened sufficiently to respond to the stimuli presented to them. Pandit (847) found no relation between the duration of sedation and the duration of amnesia produced by lorazepam. Wilson and Ellis (1157) and Kothary et al. (606) observed equal sedation with 20 mg of diazepam and 2, 3, or 4 mg of lorazepam, but greater amnesia with lorazepam; Kothary et al. (606) also noted a strong relation between dose of lorazepam and ability of patients to recall stimuli, but no relation between dose of lorazepam and sedation. Juhl et al. (547) noted a relation between impairment of recall and observable drowsiness in patients 8 h after oral administration of flurazepam (15 or 30 mg).

2. *Effects in normal volunteers.* Whereas studies on the amnesia-inducing effects of benzodiazepines on patients preparing for surgery were frequently concerned with the practical effects of these drugs, studies on normal volunteers were more often concerned with the effects of benzodiazepines on more theoretical aspects of learning and recall. There are several popular models of learning and recall; most of them emphasize the time-dependent nature of forgetting. Procedures that impair recall should be sensitive to any delay imposed between presentation and recall of stimuli. A drug that enhances the effect of a delay, or whose effects are enhanced by a delay, is likely to alter what is normally considered recall. Because of the critical interaction between drug and time in studies of drug-induced recall deficits, the reviewed studies have been arranged methodologically on the basis of the time interposed between presentation of the stimuli and the requests for recall or recognition. If the requests for recall were made immediately after the presentation of the stimuli, the study is referred to as one of immediate recall. If a delay was interposed, and particularly if the time between presentation and recall of the stimuli was varied as part of the experimental procedure, the study was referred to as one of delayed recall. Although it is useful here for purposes of organization, this division can be fairly arbitrary, since the delay between presentation and recall of the initial segments of a long list of stimuli could be longer in an immediate recall situation than the delay between presentation and recall of a short list of stimuli in a short-delay procedure.

a. IMMEDIATE RECALL. Immediate recall procedures typically required the subject to repeat or write down a series of digits immediately after they had been read or shown to him. The number of digits read varied from study to study, and word lists rather than digit lists were frequently used; some studies used both words and digits.

A number of investigators reported that oral diazepam impaired immediate recall. Doses of 5 and 10 mg produced significant or nearly significant disruption in tests of immediate recall performed 1 to 2.5 h following drug administration. A dose of 2.5 mg was less effective, and the effects of active doses had worn off in 5 to 6 h (607, 435, 517, 428, 543). Intravenous diazepam (7.5 mg) also produced impaired immediate recall of word lists 5 to 25 min after drug administration (321, 916).

Oral administration of other benzodiazepines has also been reported to disrupt immediate recall. Temazepam (20 mg) and nitrazepam (5 or 10 mg) disrupted immediate recall of digits or words (647, 1069, 542). Subhan (1059) evaluated the effects of 10, 20, 30, 40, and 60 mg of clobazam and of 5, 10, 15, 20, and 30 mg of diazepam in three different tests of recall. At least one of these tests appeared to have been an immediate-recall test. Relative to diazepam, higher doses of clobazam were required to disrupt recall of digits, suggesting that clobazam may have less effect on recall than some other benzodiazepines. Unfortunately, the doses of the two benzodiazepines were not equated on an independent test.

Lorazepam (1 or 2 mg) produced slight decrements in immediate recall, which were less at 45 min than at 3.25 h (292). Loprazolam (1 mg) also impaired immediate recall in a poorly described "name-and-address" test of short-term recall (740). Liljequist et al. (650) evaluated the effects of chronic (2 wk of administration 3 times a day) oral administration of 5 mg of chlordiazepoxide lactam, 10 mg of N-desmethyldiazepam, 15 mg of oxazepam, or 20 mg of methyloxazepam. Testing was started 50 min after the last administration of drug. Chlordiazepoxide lactam and N-desmethyldiazepam both produced impairment of immediate recall; oxazepam and methyloxazepam did not.

Subhan and Hindmarch (1062) evaluated flunitrazepam (1 mg), triazolam (0.25 mg), and lormetazepam (1 mg) on a scanning task in which subjects, after seeing a series of digits, had to indicate whether each of a second series, shown them starting 2 s later, was on the original list. The authors did not say whether the drugs produced increased errors on this task, but emphasized the increased response times produced by flunitrazepam and triazolam. They offered several interpretations of the

effects in terms of proposed recall stages; however, they did not consider the possibility that these drugs could have produced the decreased response times without affecting any process associated with recall.

A few studies have reported little effect of orally administered benzodiazepines on immediate recall. Tofisopam [100 mg (1000)], triazolam [0.125, 0.25, and 0.375 mg (121)], diazepam [10 mg (1000) or 5, 10, or 20 mg (1101)], clobazam [15 mg (849)], nitrazepam [5 and 10 mg (6)], and flunitrazepam [0.5 and 1 mg (621) or 0.25, 0.5, and 0.75 mg (121)] have all failed to produce deficits in immediate recall on a variety of tests and at a variety of postdrug test times.

Neither triazolam (0.25 mg) nor flurazepam (30 mg) altered performance on simple, forward recall of digits, whereas flurazepam did affect behavior when the digits were to be immediately recalled in the reverse order of their presentation (464).

b. EFFECTS OF DELAY ON RECALL. Some investigators have utilized several tests of recall function to evaluate the effects of benzodiazepines on remembering. Frequently, in a single study, measures were taken of both immediate recall and recall of stimuli presented as long as weeks earlier. Comparisons between delayed and immediate recall may have been confounded by factors such as level of benzodiazepine in the blood, interference by other stimuli, or the type of material learned, which may have been quite different in tests of immediate as compared to delayed recall. Nevertheless, although Scharf et al. (978) found no impairment in immediate or delayed recall following administration of clorazepate (7.5 mg or 15 mg), and Thompson and Trimble (1084) found a similar lack of effect following 2-wk administration of 30 mg/day of clobazam, a much more common finding was a disruption in delayed recall with less, or little, disruption in immediate recall. Several investigators have reported these differential effects with diazepam following delays ranging from 20 s to 25 min to 1 wk (192, 405, 355, 352, 671, 678). The study by Grove-White and Kelman (405) is particularly noteworthy, since it demonstrated a lack of effect of diazepam (0.05 mg/kg) on tests of recall made 4 s after stimuli presentation, but a significant impairment if the test was given 20 s after stimuli presentation.

Ghoneim and colleagues utilized a recall test that measured immediate and delayed (70 to 160 min) recall of 24- and 16-word lists (676, 350). There was a dose- and time-dependent impairment in recall of the words in the lists. Two indices suggested that delayed recall was more impaired than immediate recall: in the immediate recall test, the words from the beginning of the list were recalled less well than words from the end of the list; and fewer words were recalled in the delayed recall test than in the immediate recall test.

Chronic, 21-day administration of approximately 0.2 mg/kg/day of oral diazepam led to incomplete tolerance to the effects of the drug on immediate and delayed recall of word lists. Immediate recall of word lists was less impaired following chronic administration of diazepam than following acute administration, but was more impaired than following administration of placebo. Effects on delayed recall (15 min after presentation) were more pronounced under both acute and chronic conditions; less recovery was found with chronic administration using delayed recall tests than with immediate recall tests (353).

Studies of the effects of benzodiazepines other than diazepam on delayed recall have indicated that this test is sensitive to disruption by these drugs in general. A greater effect of drug administration on delayed as opposed to immediate recall has been reported with lorazepam given intravenously (135) or orally (135, 979, 978, 672, 690, 46). Intravenously administered lorazepam (3 mg) disrupted delayed recall of word lists for a longer time than did similarly administered diazepam (7.5 mg). Neither drug affected immediate recall of digits (137). Subhan and Hindmarch (1061) reported a marked effect of midazolam (15 mg) on immediate recall of word lists; the effect was even more marked when recall of the words was requested 9 h later. Delayed recall was disrupted by lower doses of triazolam than was immediate recall, suggesting a greater sensitivity of the delay procedure to triazolam, in subjects with histories of drug abuse (925). A number of studies evaluated the effects of benzodiazepines on immediate and delayed recall when the drugs were administered as hypnotics to subjects without sleeping problems. Drugs were usually given at bedtime; the subjects were awakened approximately 3 h after drug administration and given a series of tests that included measures of immediate recall. The subjects returned to sleep and were tested for recall of the same stimuli in the morning. Morning recall of the specifics of the tasks was disrupted by flunitrazepam [2 mg (82)], flurazepam (30 mg), lorazepam (4 mg), and triazolam [0.4 mg (938)]. These last three drugs and temazepam (30 mg) also impaired immediate recall at the 3 h postdrug evaluation time (938, 941). Sarcone et al. (972) found that chlordesmethyldiazepam (2 mg) at bedtime produced disruption in immediate digit and word recall tests 3 h later and had even more severe effects on delayed recall, evaluated in the morning.

Because of specific interest in the effects of hypnotic drugs on recall, Roth and colleagues (929, 928, 942) tested benzodiazepines in a paradigm similar to that described above. When the subjects were awakened 3 h following bedtime drug ingestion, they were presented with several "clinically relevant" situations. For example, they were given several candy pills to take or asked to put on various articles of clothing. They were asked to recall specifics of the situations such as the number and color of the pills, or the articles of clothing and the sequence of dressing, both immediately after the situation was presented and the next morning when the subjects awoke. A number of benzodiazepines was tested using

this procedure, including flurazepam (30 mg), lorazepam (4 mg), triazolam (0.4 mg), temazepam (30 mg), and lormetazepam (1.5 mg). Each was given on two consecutive nights. Flurazepam and lormetazepam produced the least impairment, blocking delayed, morning recall only. Each of the other drugs produced impairment of both immediate and delayed recall of the stimuli; delayed recall was impaired more than immediate recall (929, 928, 942).

In the study by Roth et al. (938), the disruption in recall in the morning appeared greater if the subjects returned to sleep quickly following the original test. The possibility that sleep itself affects recall was tested more directly by Roehrs et al. (930). Subjects who had been given 0.5 mg of triazolam at bedtime were awakened 3 h later for presentation and recall testing, following which they were required to stay awake for an additional 15 min. The investigators found that, under these conditions, the effects of triazolam were markedly attenuated when tested the following morning. This supported their hypothesis that sleep, as well as drug administration, interfered with recall.

Administration of triazolam (0.25 or 0.5 mg), lorazepam (4 mg), or flurazepam (30 mg) for six consecutive nights resulted in morning recall losses that were sustained across the administration period (930).

A number of studies has evaluated delayed recall alone. Healey et al. (447), who presented subjects with lists of six words and tested for recall 5 min later, reported that lorazepam (1 or 2 mg) disrupted recall. Maximum effects were obtained in the last test period, 120 min following drug ingestion. Diazepam (5 or 10 mg) and clorazepate (7.5 or 15 mg) had no effects.

Clarke et al. (176) found that i.v. diazepam (0.24 mg/kg) produced a profound impairment of recall of word lists 1 to 1.5 h after their presentation. Clarke et al. (175) reported that 1 h after i.v. administration of either diazepam (0.28 mg/kg) or flunitrazepam (0.014 mg/kg), subjects had a nearly total inability to recall a list of words they had categorized immediately following the drug injection. Intravenous administration of midazolam (5 mg) produced amnesia for postcards shown over a 60- to 90-min period and tested 6 h later (258).

Kleindienst-Vanderbeke (584) reported clobazam (30 mg) and lorazepam (3 mg) produced deficits in recall, when tested 100 min after subjects learned various types of verbal and nonverbal material.

Clark et al. (171) used an interesting and unique experimental design to determine when recall was most impaired following administration of i.v. diazepam. The subjects' task was to indicate which 50 of a group of 100 words were "old" words, i.e., words they had heard before in the experiment, and which were "new words." A list of 150 words was read to them prior to beginning the task, to provide an initial source of "old" words. Blocks of 100 words were presented for identification every 14 min (9 min for presentation and test; 5 min between blocks). The source of "old" words for each block except the first was "new" words that had been presented two blocks, or approximately 28 min, earlier. Diazepam (10 mg) was delivered intravenously after the third block. Subjects showed improved ability to designate the words correctly as "old" or "new" across the first three blocks, i.e., those prior to diazepam administration. Further improvement was shown on the first two blocks after diazepam administration, i.e., when the "old" words were those that had been presented prior to administration of diazepam. A marked decrement was shown on the third block, 42 min following i.v. administration of diazepam. The "old" words in this block were those that had been first presented in the 14- to 25-min block following diazepam administration. Recovery of the ability to designate words correctly continued over the next hour of the experiment. The authors interpreted these results as indicating a diazepam-induced impairment of storage of new information, occurring 14 to 25 min following i.v. drug administration, and measured 35 to 54 min later. The authors also noted that retrieval of previously stored information appeared unaffected by diazepam.

c. RETROGRADE AMNESIA. Several studies have tested recall of word lists presented prior to, as well as after, administration of benzodiazepines. Rarely was a deficit observed in recall of stimuli presented prior to drug administration. Usually, no retrograde amnesia was noted (674), and frequently an improved recall of words learned prior to drug administration was reported (257, 176, 481, 137, 192, 348, 136, 676). Although this improved retention of material presented prior to the drug was often regarded as paradoxical, it occurred so frequently that it can be considered a rather typical effect of these drugs. Improved recall of information presented prior to drug administration would occur if learning of material subsequent to drug administration were restricted, i.e., if retrograde interference produced by learning the new material were reduced. This possibility was tested directly by evaluating recall of a list of words learned prior to drug or placebo administration, under conditions in which zero, one, or two lists were presented for learning after drug or placebo administration. Relative to placebo conditions, diazepam enhanced learning of the predrug list only if a second or third list was presented following drug administration (349, 480). The lists presented after drug or placebo administration served to interfere with recall under the placebo condition (retroactive interference), but not following diazepam administration. This was good evidence that diazepam impaired the acquisition of material presented following its administration, rather than simply impairing behavior that indicated acquisition.

d. ACQUISITION. This section considers studies of the effects of benzodiazepines on recall in situations in which subjects were exposed to more than one opportunity to learn the material before recall was requested. As applies also to studies of immediate and delayed recall, the

process of acquisition may include performance, sensory, and other factors that could be altered by the drug, apart from its effects on learning or recall. The data are described simply as the change in the number of trials or the time required to meet the criterion of acquisition performance following drug administration. The type of tests that have been used to evaluate acquisition deficits varies enormously, from learning simple lists of words to much more complicated tasks.

Deficits in learning of lists of words or numbers, or associations between, for example, words, pairs of syllables, or shapes and numbers have been demonstrated following administration of oral or i.v. diazepam [0.2 to 0.3 mg/kg (176, 481)]. In at least one experiment, however, no effect of diazepam (10 mg) on acquisition was observed (649). Once material was learned, diazepam did not affect retention (860, 859).

Other benzodiazepines have also been found to disrupt acquisition of new material. Temazepam (20 mg) produced increases in the number of trials necessary to learn verbal material (648). Nitrazepam (5 mg) impaired acquisition of associations among groups of three words (276).

The effects of chronically administered benzodiazepines on acquisition of verbal material have been evaluated by several investigators. In two studies, the effects of chronic, but not acute, administration of benzodiazepines were measured on tests of acquisition of verbal material. Bromazepam (6 mg), given 3 times daily for 2 wk, produced increases in the number of errors made on these tests (646). Chronic administration of chlordiazepoxide lactam (5 mg), but not N-desmethyldiazepam (10 mg), oxazepam (15 mg), or methyloxazepam (20 mg), produced learning deficits (650). Since learning was not tested following acute administration of these drugs, the possibility of tolerance development was not measured. Acquisition of a verbal-learning task was impaired by acute administration of diazepam (10 mg), but not after chronic (2-wk) administration of this dose of the drug (645), suggesting that tolerance can develop to the effects of benzodiazepines on acquisition.

A procedure of "selective reminding" was used to evaluate the effects of alprazolam (1 mg) and lorazepam (2 mg) on learning of lists of words. In this task, lists of words were read to the subjects, and they were requested to recall them. Any words not recalled were repeated, and recall of the entire list was requested. This was continued for ten trials. Both drugs decreased the number of words learned; the effect of alprazolam was more rapid in onset and shorter in duration than that of lorazepam, and it produced a slightly greater acquisition deficit (91).

The effects of i.v. diazepam, 5 mg or more, were evaluated using an operant procedure that included acquisition of new response sequences and performance of previously learned response sequences. Two of the three subjects showed greater drug-induced disruption of acquisition than performance, whereas in the third subject diazepam impaired both acquisition and performance (226).

A few studies have evaluated the effects of benzodiazepines on learning and recall using unusual tasks. Photiades et al. (869) measured the capacity of chlordiazepoxide (5 mg) to affect memorization of poetry, memorization of logical figures, recollection of landscape photographs, learning of nonsense syllables, and recollection of a story. The drug had no effect on any of these tasks, perhaps because of the small dose used.

Hrbek and coworkers used a test of "artificial conditioned speech connections" to evaluate the effects of benzodiazepines on learning. The task was acquisition of associations between objects, sounds, or tactile stimuli and an artificial, two-syllable "word." Six stimulus-"word" pairs were presented at least 8 times, or until the subject responded correctly to all six. The number of repetitions necessary to acquire the connections was increased by diazepam (10 mg) 1 and 2 h after administration. Diazepam also produced increases in the number of errors made during acquisition and slowed responding (496, 497, 494). When diazepam (10 mg) was delivered subcutaneously, its effects on artificial speech connections lasted only 1 h (495, 497). Chlordiazepoxide (30 mg) was evaluated in a similar test and also produced impairment in the various indices, although it was apparently not as significant as that produced by diazepam (493). Oxazepam, given orally, was effective only at 2 h after administration (497, 498).

e. STATE-DEPENDENT LEARNING. The theory of state-dependent learning and recall has also been applied in several studies of the effects of benzodiazepines. The theory holds that material learned under one state, either drugged or nondrugged, will be recalled more readily in that same state. Although there have been several tests of this theory using benzodiazepines in humans, none has clearly demonstrated the effect. A limited state-dependent effect has been reported by a number of investigators (644, 645, 860, 529). Since very large doses of sedatives are required to produce clear state-dependent effects in animals (837), it is possible that insufficiently high doses were evaluated in humans. This suggests, however, that, if the benzodiazepines can exert state-dependent effects on learning and recall, such effects following administration of therapeutic doses are unlikely to be significant.

3. Recall in anxious subjects. The studies described above clearly indicate that virtually all tested benzodiazepines can impair the ability of healthy individuals and patients preparing for surgery to remember events occurring after drug administration. Healthy individuals and surgery patients are not, however, representative of most people who receive benzodiazepines, who suffer from problems of anxiety and insomnia. Anxiety itself may affect learning and recall, and it is possible that the benzodiazepines will improve rather than impair recall

in this population. On the other hand, the benzodiazepines may produce recall disturbances in patients being treated for anxiety, as they do in healthy patients; this would represent an undesirable side effect of which patients should be aware.

Some studies of the effects of benzodiazepines on recall in anxious subjects have used subjects with clinically demonstrable anxiety. A few case studies, for example, have indicated that recall was impaired in patients taking high doses of benzodiazepines for treatment of anxiety (411, 357).

Some experimental studies of clinically anxious subjects have found similar detrimental effects of diazepam on recall. Hartley et al. (436) evaluated the effects of diazepam (5 mg) on performance of subjects who showed high or low levels of anxiety on the Spielberger test of state-trait anxiety (1030). The task was different from many of those described earlier; subjects were given a category (e.g., fruit) and a letter and asked to name a member of the category that started with that letter. At a later time, they were asked to recognize items in the selected category. The anxious subjects responded more slowly than the nonanxious subjects in both recall and recognition of category items, and their speed was decreased even more by diazepam. Thus, diazepam exacerbated the effects of anxiety in this test, although it was not clear that this was a recall as opposed to a performance deficit.

A "running memory" task was used by Barnett et al. (47) and Desai et al. (224) to evaluate recall disturbances in subjects with high or low levels of anxiety as measured by the Spielberger test. A series of consonants was presented one at a time to the subjects, who were unaware of the length of the lists. At the sound of a tone, they were to recall the last eight consonants presented. Subjects with high measured levels of anxiety made more errors than subjects with low levels of anxiety in one form of this task (consonants presented at a slow rate of speed with subjects required to say the word "the" repeatedly during the presentation). Diazepam (5 mg) improved the performance of the more anxious subjects. Diazepam produced a nonsignificant impairment in the performance of the less-anxious subjects. These were very interesting results, among the few that suggested a detrimental effect of anxiety on recall and an improvement of recall in anxious subjects following administration of a benzodiazepine.

The effect of baseline levels of anxiety on the capacity of a benzodiazepine to alter recall was shown rather dramatically in a study by Koeppen et al. (591). Twelve male and 12 female subjects were given several recall tests, as well as the Spielberger test of state-trait anxiety. Following placebo administration, the more-anxious males did more poorly in a test of figural recall (recalling a city map 1.5 h after it was shown) than did the less-anxious males. The recall of the anxious males was improved by clobazam (30 mg); that of the less-anxious males was not greatly affected by the drug. In contrast, under placebo conditions, the more highly anxious females performed better in the recall task than did the less-anxious females, and clobazam (30 mg) produced a decrement in recall by the more-anxious females. Behavior of females with low anxiety was relatively unaffected by drug administration.

Clobazam was compared to lorazepam in subjects who reported anxiety problems. The subjects were evaluated with a number of tests, one of which was an acquisition test. The patients received 10 mg of clobazam, 1 mg of lorazepam, or placebo twice daily for 9 days. Although both the clobazam and the lorazepam groups showed decreased anxiety and improved performance over the 9-day period, the same effects were shown also in the placebo group. It was not clear whether the improved learning of the subjects was due to decreases in anxiety or to practice effects (818).

Two studies have examined the effects of benzodiazepines on immediate and delayed recall of subjects who were receiving benzodiazepines, primarily for anxiety disorders. In the study by Angus and Romney (18), subjects were tested under conditions in which they had either been drug free for at least 2 wk or when they had been taking diazepam daily for at least 5 days. Doses of from 5 to 30 mg of diazepam produced impairment on a delayed recall test (recall of words that had been learned to a critierion 24 h earlier). Immediate recall was unaffected. Interestingly, there was a dose-related decrease in anxiety produced by diazepam, but the effects on recall were inversely related to the dose. Lucki et al. (681) evaluated the effect of benzodiazepine medication on immediate and delayed recall of word lists in 22 chronic benzodiazepine users (average of 5 yr of use). Sixty to 90 min after taking their prescription benzodiazepine (diazepam in nine, lorazepam in six, clorazepate in four, alprazolam in two, and chlordiazepoxide in one subject), immediate recall was not impaired. Delayed (20-min) recall, however, was significantly impaired in these subjects, regardless of the medication taken. No other tests of performance continued to be affected by the prescribed benzodiazepine. This indicates that tolerance may not develop to the impairment of recall produced by these drugs. This indication is supported by the rather anecdotal observation of Busto et al. (150) that some patients who were referred to the investigators' clinic for discontinuation of long-term use of benzodiazepines were bothered by recall problems associated with use of the drugs.

Uhlenhuth et al. (1101) used a scanning task to measure recall in normal subjects; a series of from one to six digits was shown, and then, following a signal, single digits were shown. The subjects were asked to indicate whether each single digit had been on the original list. Reinforcement was provided, based on speed and accuracy of performance, as either an indication of money earned, or actual presentation of money. Although sub-

jects in this experiment were not selected for having high anxiety, they reported being anxious, apparently because of the requirements of speed and accuracy in the task, and because of the reinforcement contingencies. Diazepam (5, 10, and 20 mg) reduced reported anxiety at the same time that it decreased errors on the scanning task. The improvement on the task was not dose related.

4. Effects in insomniac subjects. As in the case of treatment of anxiety, the use of benzodiazepines to treat insomnia could result in improved learning and recall if insomnia resulted in deficits of learning and recall, or could result in impairment of learning and recall as predicted from the effects of these drugs in healthy subjects. Studies of the effects of benzodiazepines on recall in subjects with reported sleep disturbances have not allowed a firm conclusion to be drawn on this issue. Although a number of studies have reported recall deficits produced by benzodiazepines in subjects with sleep disturbances (e.g., refs. 977, 770, 169, 516, and 1031), the reports did not indicate that the studies took account of possible baseline differences in recall abilities between insomniac and normal subjects, prior to or after drug administration. When baseline ability to recall material did not differ between normal and insomniac subjects, the effects of the drugs seemed virtually identical.

Only one study was found that evaluated recall deficits in insomniac as compared to normal subjects. Peck et al. (853) administered nitrazepam (2.5, 5, or 10 mg) at bedtime to groups of light sleepers and sound sleepers. Tests of immediate recall, auditory vigilance, auditory reaction time, and mental sedation were conducted the following morning. The light sleepers made more errors than the sound sleepers on the recall task under the placebo condition, although the significance of this difference was not emphasized and apparently not tested. Nitrazepam produced a dose-related increase in the number of errors made by the sound sleepers. Low doses of nitrazepam produced very slight decreases in errors made by the light sleepers. The highest dose of nitrazepam produced recall disturbances that did not differ between the two groups.

5. Effects in elderly subjects. Recall in patients with anxiety or insomnia could be enhanced by administration of benzodiazepines if these pathological states resulted in decreased recall; older subjects, who may have greater recall deficits than younger subjects in the absence of drugs, might be even more impaired following benzodiazepine administration. Amnesia resulting from administration of flunitrazepam (0.01 mg/kg) i.v. was evaluated by Korttila et al. (604) in 79 patients of various ages who were being prepared for bronchoscopy. They found large differences among the age groups in the onset and duration of the amnesia produced. Patients over the age of 60 showed a more rapid onset and longer duration of amnesia than those younger than 60.

Measures related to learning and recall were also evaluated in groups of 12 young (mean age, 25.9 yr) and 12 older (mean age, 70.4 yr) subjects by Pomara et al. (878). Prior to drug administration, the older subjects were more impaired than the younger subjects in tests of reaction time, delayed recall, and immediate and delayed recall of items presented in a "selective reminding" task similar to that described earlier. The older subjects were also more impaired than younger subjects in these tasks 1 h after administration of a low dose of diazepam (2.5 mg). This dose of diazepam also produced more reports of unspecified "symptoms" on a self-report symptom rating scale in the older subjects at both 1 and 3 h postdrug. Plasma diazepam levels were elevated in the older subjects at 1 h following drug administration, but there was no correlation in either subject population between the amount of impairment and plasma levels of diazepam.

Scharf et al. (976) found no effect of clorazepate (3.75 or 7.5 mg) on delayed or immediate recall of word lists by subjects aged 60 to 74 yr. This group had found a similar lack of effect of these doses of clorazepate on recall of younger subjects and suggested that this benzodiazepine may have less profound effects on recall than other benzodiazepines.

6. Summary and discussion. Studies of presurgical patients strongly suggest that benzodiazepines can impair recall of events that follow their administration (anterograde amnesia). By their nature, however, these studies suffer from several drawbacks. Placebo controls and double-blind procedures were rarely used in evaluations of surgical patients. Likewise, the time between administration of the drug and presentation of the stimuli, as well as the time between presentation of the stimuli and requests for recall of them, varied from study to study. Also, a relatively limited number of benzodiazepines (diazepam, flunitrazepam, and lorazepam), typically those indicated for use prior to surgery, have been studied in these procedures. Despite these drawbacks, the results of these studies are quite consistent in demonstrating impairment of recall that is related to both dose and route of administration.

These studies indicated differences among the drugs in the degree of amnesia produced and in the route of administration that resulted in consistent amnesia. Diazepam and flunitrazepam were not very effective in producing amnesia when they were given orally or intramuscularly. However, these benzodiazepines were rapidly effective, with a short duration of amnestic action, when given intravenously. Lorazepam, on the other hand, produced amnesia by all three routes of administration. Its onset was much slower, even when given intravenously, and its duration of action was relatively prolonged.

Although amnesia can be considered a beneficial effect of a drug given prior to surgery, it is an unwanted side effect if it develops in patients receiving these drugs for anxiety, insomnia, or somatic problems. To understand better this potentially adverse effect of this class of drugs, it is important to evaluate them under more carefully

designed experimental conditions and in normal volunteers or subjects who resemble more closely those who would receive these drugs as treatment, or who may be particularly susceptible to the amnesia-inducing properties of these drugs.

Studies in normal volunteers have demonstrated clear detrimental effects of benzodiazepines on the ability to recall stimuli presented after drug administration. The deficits are greater if there is a delay between the time the stimuli are presented and the time that recall is requested. Since the definition of memory processes includes their reduction over time, the fact that benzodiazepine effects on recall are enhanced by the passage of time indicates that these drugs may be affecting memory processes themselves, as opposed to affecting the ability of the subjects to perform the recall task. This is further supported by the frequent findings of enhanced recall of events occurring prior to drug administration, indicating that the benzodiazepines prevent interference from events that occur following drug administration.

Benzodiazepines also appear to retard acquisition of material. However, studies of this effect rarely controlled for possible effects on performance as well as did studies of effects on learning; when such controls were included, the evidence appeared suggestive rather than definitive with regard to specific effects of benzodiazepines on acquisition.

Evidence for a state-dependent effect of benzodiazepines on recall is slight at best, and state dependency appears unlikely to be a significant factor with respect to the effects of therapeutic doses on recall.

Some of the studies of the effects of benzodiazepines on recall in anxious subjects suggest that these drugs may improve recall if recall is impaired due to anxiety. Nevertheless, reports of recall disturbances in patients receiving benzodiazepines for treatment of anxiety indicate that recall disturbances remain a problem for some of these patients. Tolerance to the disrupting effects of benzodiazepines on recall apparently does not develop to the same extent as it does to other behavioral effects of the drugs. Interestingly, the data indicate that, in the clinical population, as in the normal population, immediate recall is disrupted less than delayed recall by these drugs.

The benzodiazepines also impair recall in insomniac subjects. Disturbances in recall are apparently not long-lasting, disappear with continued drug administration, and are generally not profound when the drug is administered at bedtime and measures of recall function are taken in the morning. Thus, there may be little reason for concern that patients receiving benzodiazepine hypnotics will suffer from prolonged or severe disturbances in recall. What remains to be determined is whether recall ability might improve with the administration of low doses of benzodiazepines to subjects with insomnia. The evidence for this is suggestive, but far from conclusive; further research in this area is certainly required.

D. Effects of Benzodiazepines on the Risk of Accidents

Concern about the possibility that benzodiazepine use may increase the risk of accidents was prompted by an early report by Murray (799), who found that 68 drivers treated with chlordiazepoxide were involved in 16 road accidents, representing a 10-fold increase over the rate projected for normal drivers; this investigator also reported 3 falls resulting in bone fracture among 116 similarly treated patients.

A substantial number of studies have examined this potential risk of benzodiazepine use, most of which have focused on the possible contribution of these drugs to increased risk of automobile accidents. These have included experimental studies of simulated and actual driving behavior, as well as epidemiological investigations of drug use among subjects detained for driving while intoxicated and among subjects involved in actual accidents. In addition, a few studies have examined the role of benzodiazepine use in the incidence of accidents other than automobile accidents.

Previous publications and reviews of interest relevant to the effects of minor tranquilizers on the risk of traffic accidents include those by Joscelyn et al. (544), Willette and Walsh (1144), Bauer (54), and Landauer (632). The reader may also be interested in a somewhat earlier publication by Edwards (266) regarding the effects of sedatives and hypnotics on the risk of occupational accidents, as well as on driving.

1. Effects on the risk of automobile accidents. a. EXPERIMENTAL STUDIES. In consideration of experimental studies of drug effects on driving-related behaviors, the question of validation of procedures is inevitable. Studies of "actual" driving behavior after drug ingestion are typically conducted on a closed course at low speeds, or with a driving examiner at the side of the subject; these procedures may generate behaviors that may not be a function of the same variables as driving behavior in the natural setting (75, 657). The primary question regarding simulated-driving studies, obviously, is how closely analogous to "real" driving is the simulation; if the simulation is closely analogous, the simulated driving should be affected by drugs much as would "real" driving. Laboratory studies, including many of those reviewed above (section IV B 1, pages 290 to 294), frequently claim to be examining "skills related to driving," although the relationship often is neither apparent nor documented. In fact there is evidence that laboratory performances are not (178, 1012, 265, 631), or not always (421), related to actual driving performance; and it is questionable whether drug effects observed in these studies have any bearing on how actual driving performance would be affected by these drugs (632).

There has been considerable debate over the proper design of studies designed to be predictive of driving in the natural setting; this debate will undoubtedly continue. Further research may shed light on the relative

potential of each of these types of studies to help establish whether and to what extent drug use contributes to traffic accidents.

i. Driving simulation studies. Driving simulators vary in complexity and in how closely they approximate real driving conditions. Most simulators combine some tracking task with a reaction-time test. Acute administration of diazepam (10 mg; the drugs in this study and those described below were administered in their oral forms) produced an increase in errors in tracking tasks and an increase in reaction times (1154), although one study found effects of lormetazepam (2 mg) but not diazepam (10 mg) on tracking and reaction time (1155, 1154). With other simulators, diazepam (10 mg) increased the incidence of neglecting instructions and the incidence of collisions (663, 665). No effect of diazepam on driving simulation was observed the next day after 5 mg had been given at bedtime and another 5 mg were given immediately before the test (769). In a complex simulation, diazepam (8 to 16 mg) increased variability of lane position in curve following, adjusting for wind gusts, following a lead car, and following a lead car with wind gusts; diazepam also increased speed variability in curve following and adjusting for wind gusts as well as increasing errors in swerving or stopping for obstacles (1022). With repeated administration, diazepam (15 mg per day for 9 days) increased lane position and speed and decreased slalom speed, target detection, and wind gust control (790, 1021). Chlordiazepoxide (20 mg per day for 1 wk) increased speed and decreased accuracy of tracking (763). Treatment with lormetazepam (2 mg) or flurazepam (30 mg) for 7 days at bedtime increased reaction time, whereas only flurazepam decreased correct responses in tracking (1153).

In summary, simulated driving performance of normal subjects was affected by several of the benzodiazepines administered in single therapeutic doses. Diazepam (10 mg) has been studied frequently and has been found either to increase (1154, 665, 663) or not to affect (769, 1155) errors in maintaining lane position or tracking. Additionally, there have been reports that, after diazepam, subjects neglect instructions (665, 663). Other studies have shown occasional effects of 10 mg of diazepam, including: increased speed (663); increased reaction times (1154); inability to maintain heading after simulated wind gusts (1022); and increased collisions (665). One study showed a variety of effects of diazepam given as 10 mg at night and 5 mg the next morning before the test (790). Other benzodiazepines that have been shown to adversely affect tracking and reaction times in driving simulator performances at therapeutic doses are lormetazepam (1153–1155) and, after repeated doses, chlordiazepoxide (763) and flurazepam (1153, 1154).

ii. Studies of "actual" driving behavior. Studies of the effects of benzodiazepines on actual driving performance can be divided into those studies that examine subjects' ability to navigate an automobile through some test course in which various types of tasks are required, and those in which driving takes place under circumstances intended to approximate traffic situations. Typical test courses include parallel parking; slalom in a forward gear and occasionally in reverse; and estimating, as well as attempting to drive a vehicle through, the narrowest passable gap. Each of these tasks is scored on some basis, such as the number of times a pylon is hit or time taken to complete the task.

Kielholz et al. (578) found no significant effects of 20 mg of chlordiazepoxide on errors (pylons hit) or time to complete a driving course. During the test, subjects were required to react to different stimuli by activating right- or left-turn signals. Although reaction times were not affected, there was an increase in errors of turn signaling. A lower dose of chlordiazepoxide (10 mg) did not affect driving performance (577).

Wetherell (1133) examined the effects of 10 mg of diazepam in variations of the gap test. In the various procedures, subjects attempted to drive through gaps of different sizes regardless of whether they thought the gaps large enough to pass (skill); subjects indicated whether they thought various gaps passable, without attempting them (confidence); and finally subjects themselves set the narrowest gap they thought passable and then attempted the gap. Although the diazepam and placebo groups on average did not differ in their ability to pass the different gaps in the test of skill, there were different effects among individual subjects, with some performances improving and some deteriorating. There was no effect of diazepam on the confidence test, again with differences between individual subjects, and, in the last test, the diazepam subjects set the gaps wider than the controls did. The author interpreted the results as suggesting that the subjects became more cautious after diazepam administration.

Hypnotics administered the evening before a driving test have also been shown to affect driving-test performance. Betts and Birtle (72) gave flurazepam (15 mg) or temazepam (20 mg) and found an increase in the number of pylons hit after either drug, with neither a change in the speed of driving nor a decrease in the detection of passable gaps. Flurazepam also increased the number of pylons hit in a slalom course. In contrast, midazolam (15 mg) given on the previous night had no effect on performance in a gap test, forward car alignment, or braking reaction time (479).

Several investigators have examined the effects of benzodiazepines given repeatedly for varying durations. Betts et al. (73) gave five 10-mg doses of chlordiazepoxide over a 36-h period. Success in a gap test decreased for the female subjects, while time taken to complete a slalom increased for males without affecting accuracy. There was no effect on either sex in a parking test. Clayton et al. (179) gave the same dose regimen of chlordiazepoxide and found no effects on gap estimates or parking in either sex and an increase in time to

complete the slalom in males but not females. The selective effect on slalom performance in males may be due to the fact that males tend to complete the slalom faster than females in the absence of drugs (73); this higher speed among males may render drug-induced errors more likely.

Hindmarch et al. (475) gave 20 mg of clobazam at bedtime over a 6-day period and tested subjects on awakening after the sixth dose. In a later study, Hindmarch and Gudgeon (474) compared clobazam (10 mg) and lorazepam (1 mg) given 3 times per day over a 3-day period and tested subjects after administration of the first dose on the fourth day. Clobazam had no effects on performance in any test, whereas lorazepam increased reaction times in braking and increased errors in parking, three-point turns, and slalom negotiation.

A few studies have examined drug effects on driving an automobile in real traffic or highway conditions. Using an instrumented automobile, O'Hanlon et al. (822) found that diazepam (10 mg) increased variability of lateral position in a traffic lane. Similar results were obtained the morning after the second night of treatment with flurazepam (15, 30 mg) and loprazolam (1, 2 mg) in female subjects with a history of hypnotic use (821). After seven nights of flurazepam administration, the variability in lane position persisted but was less marked (820). After treatment for 7 days with temazepam (20 mg) or flunitrazepam (2 mg), the velocity with which subjects turned the steering wheel was increased above control, reflecting quick, staccato steering adjustments rather than continuous graded compensations for changing road orientations; additionally, the performance of subjects as scored by observers included a greater number of errors in technical handling (982). In another study utilizing a scoring method for evaluating driving performance, de Gier et al. (220) found that patients receiving diazepam (5 or 10 mg per day) were scored as inadequate more often than control subjects on the 22 most important items. Biehl (75) also scored driving performances after 2 days of administration of diazepam (10 mg) or clobazam (20 mg). The subjects in this study ranked high on the neuroticism scale of the Cattell Personality Factors Questionnaire. Of the 29 driving variables scored, only one (readiness to brake) was significantly affected, and the report gives no indication of how this variable was measured. Readiness to brake was decreased by diazepam and increased by clobazam.

In summary, actual driving performance of normal subjects was affected by several of the benzodiazepines administered for 1 or 2 days at therapeutic doses. Diazepam, after single doses of 5 and 10 mg, increased the variability of lane positioning (822) but had inconsistent effects on performances of different subjects in a gap test (1133). Chlordiazepoxide had no effects at doses of 10 and 20 mg (578, 577); however, five 10-mg doses administered over 36 h decreased performance in a slalom test (73, 179) but had no effects on performance in a gap test (179). Flurazepam, at doses of 15 and 30 mg, increased variability of lane positioning (821); this effect had diminished after 7 days of treatment (820). At 15 mg, flurazepam also increased errors in a slalom and gap test, but did not alter judgment regarding passability of gaps (72). Clobazam, at 10 and 20 mg for three or two nights, had no effects on slalom, gap, and braking-readiness tests (475, 474, 75). Other studies have found no effects of therapeutic doses of midazolam (479) or temazepam (982, 72) on different tests of driving performance.

b. EPIDEMIOLOGICAL STUDIES. Epidemiological studies might appear to afford a direct method for estimating the extent to which benzodiazepine use may contribute to traffic accidents. However, to arrive at such an estimate reasonably, the incidence of drug use in an accident-involved population must be compared with that in an appropriate reference group; unfortunately, it is difficult to identify a population that would serve this purpose adequately, and still more difficult to establish an effective and practical means of sampling such a population.

The benzodiazepine-using population differs from the general population in several respects, beginning with the reasons for use, such as anxiety or insomnia; benzodiazepine users are also more likely than the general population to suffer from multiple somatic health problems. Psychiatric patients can differ from the general population with respect to risk of traffic accidents, independent of drug use (cf. refs. 697 and 267); further, there have been suggestions (though no supporting data) that driving performance among such patients may be improved while they are medicated (998, 656). Patients suffering from nonpsychiatric illnesses may also differ from the general population with regard to their risk of involvement in traffic accidents regardless of whether they are using psychoactive drugs. Individuals taking psychoactive medications may also differ from the general population with respect to their tendency to take risks and may therefore be more likely to be involved in accidents than those that take fewer risks.

Apart from characteristics specifically associated with drug use, other considerations also enter into the task of identifying an appropriate comparison group. For example, those involved in traffic accidents may be driving on different roads and at different times than drivers not involved in accidents; thus, the most appropriate case-control studies sample drivers not involved in accidents who are driving at locations and times at which accidents occurred. Unfortunately, few such case-control studies have been reported. Even case-control studies, however, cannot determine whether the factors that lead to drug use increase the risk of accidents independent of the actual use of drugs.

Drug use by individuals involved in traffic accidents should be confirmed by reliable techniques of chemical detection, since self-reports are not always available and are notoriously inaccurate (e.g., refs. 9, 488, and 489). Chemical detection of drugs in body fluids, however, does

not ensure that the subject was under the influence of the drug at the time of the accident, for several reasons (297). Drug levels in biological fluids are typically not directly related to the degree of drug effect (see, for example, refs. 739 and 271). This is especially true with respect to drugs detected in urine, since urine tests can be positive after the behavioral effects of the drug have subsided. Detection of drugs in blood is preferable; however, because of the possibility of tolerance, whether acute or chronic (550), blood levels are not directly indicative of an effect of the drug on behavior. Thus, the use of chemical detection may indicate a relation between drug-taking and accidents, but cannot specify whether such a relation was causal.

Studies have focused on drugs detected in body fluids of individuals arrested by authorities for driving while intoxicated, and of individuals injured and killed in traffic accidents. These categories of individuals may be viewed as representing a progression of increasingly dire consequences and, possibly, as a roughly corresponding progression in degree of drug-induced impairment.

i. Studies of drivers detained for driving while intoxicated. Studies examining detection of benzodiazepines in individuals arrested for driving while intoxicated are shown in table 8. In studies from North America, Western Europe, Australia, and New Zealand, the incidence of benzodiazepine detection in drivers detained by authorities for driving while intoxicated has ranged from 0.8 to 11.4%. Studies of drivers who appeared intoxicated but had low blood alcohol levels (thus raising the suspicion of use of drugs other than alcohol) generally found more frequent drug-positive results (e.g., refs. 1156, 339, and 927; however, see refs. 771 and 298). In many studies, drug-positive blood samples also contain concentrations of alcohol above the level of legal intoxication (9, 1037). In addition, in reports that have specified the levels of benzodiazepines found in such subjects, these have reflected use of doses within the therapeutic range (e.g., refs. 927 and 1109).

One study (345) compared the incidence of benzodiazepine use in arrested drivers with the incidence of benzodiazepines in blood samples from surgical inpa-

TABLE 8

Studies of drivers detained for driving while intoxicated

References	Geographical area	Dates of survey	Method of detecting drugs	No.	Benzodiazepine positive (% of no.)			Notes
					(a) EtOH negative	(b) EtOH positive	Sum of (a) & (b)	
Finkle et al., 1968 (298)	U.S.A.	1966	Interview	3,409			1.2	
White and Graves, 1974 (1136)	U.S.A.	1973	Blood	705	1.4	4.5	6.0	
Peel et al., 1984 (856)	Canada	1984*	Saliva	56	0	7	7	Only 56 of 445 DWI† cases would participate.
Eakins and Faloon, 1973 (263)	Ireland	1973–4	Interview	578		3.3	3.3	
Gelbke et al., 1978 (345)	W. Germany	1974–5	Blood	2,050			2.2	Assayed for diazepam only.
Ulric: et al., 1985 (1102)	Switzerland	1982	Blood	2,971	0.3	1.8	2.1	
Neuteboom and Zweipfenning, 1984 (809)	Netherlands	1981–2	Interview	38,203			3.5	
Holmgren et al., 1985 (488)	Sweden	1981–2	Urine	1,603			11.4	
Alha et al., 1977 (9)	Finland	1974	Blood, urine	100	0	2.0	2.0	
Steentoft et al., 1985 (1038)	Denmark	1978–9	Blood	1,382	0.9	4.8	5.8	Sample not entirely DWIs.
Wilson, 1985 (1156)	Australia	1974–5	Interview	1,985			3.7	
Subjects with low blood alcohol level								
Finkle et al., 1968 (298)	U.S.A.	1966	Blood	180			2.2	
Garriott and Latman, 1976 (339)	U.S.A.	1973	Blood	64			10.9	All diazepam or chlordiazepoxide.
		1974		71			23.9	
White et al., 1981 (1135)	U.S.A.	1973–8	Blood, urine	8,116	4.6	3.8	8.4	
Valentour et al., 1980 (1109)	U.S.A.	1978–9	Blood	788			11.3	Most detections at therapeutic levels.
Robinson, 1979 (927)	N. Ireland	1973–6	Blood, urine	425	1.4	20.7	22.1	Most detections were at therapeutic levels.
Wilson, 1985 (1156)	Australia	1974–9	Blood	173			39.9	
Missen et al., 1978 (771)	New Zealand	1978*	Blood	130	0	0.8	0.8	

* Date of publication; survey date not provided.

† DWI, driving while intoxicated.

tients. The rate of positive samples for inpatients was 27%, compared with 2.2% for those arrested for driving while intoxicated. The differences in the groups compared render this finding uninterpretable.

ii. Studies of nonfatally injured drivers. The incidence of detection of benzodiazepines in nonfatally injured victims is shown in table 9. The percentage of benzodiazepine detections ranged from zero, in a study with a small sample size (62), to 20.3% (94). In many of the studies, benzodiazepines were detected in blood samples that were also positive for alcohol or other drugs.

In one study from North America (1081–1083), "tranquilizers" (mostly diazepam) were detected in blood of 8% of the victims. Blood levels were consistent with those that might be expected from use of the drugs at therapeutic doses. An analysis of the accident reports and driver interviews taken to determine accident culpability showed that the percentage of benzodiazepine-positive drivers deemed culpable for the accidents was not different from the percentage of drug- and alcohol-free drivers that was deemed culpable for the accidents.

In a case-controlled study, Honkanen et al. (489) compared blood samples from nonfatally injured drivers with those from a group of control drivers sampled from the same roads, days of the week, and times of day. Unfortunately, the control subjects were younger and more often female than the accident-involved group. In this study, the frequency of benzodiazepine detection was not statistically different in drivers involved in accidents and in control drivers. Bo et al. (736) found that the frequency of benzodiazepine-positive samples of blood from nonfatally injured drivers in Norway was 20.3%, which was significantly higher than that for a comparison group of drivers (not case controlled) attending a routine medical check-up.

Several studies have used evidence other than chemical detection, such as prescription records or subject interview, in order to assess drug use. Jick et al. (531) compared prescription records of nonfatally injured drivers, passengers, and a group whose driving status or culpability could not be determined or who were drivers deemed not at fault for accidents. All groups had comparable frequencies (7, 8, and 6%, respectively) of diazepam or flurazepam prescriptions. Skegg et al. (1016) compared prescription records of road-accident victims admitted to hospitals and randomly selected controls matched for sex, age, and other factors. Of 57 victims, 8.8% had used minor tranquilizers, whereas only 2.2% of the controls had been prescribed minor tranquilizers. Of the five victims that had been prescribed minor tranquilizers, there was no mention of alcohol in three of the cases; there was no evidence of alcohol in the blood of the one fatally injured victim. From these data, the authors estimated that the psychiatric conditions of these subjects, or the medications prescribed for these conditions, increased the risk of road accident by a factor of 4.9.

Sabey (956) interviewed injured drivers about their drug use in the 48 h prior to the accident. A control group was also interviewed; however, the control group was not comparable to the accident-involved group with regard to sampling times and locations. The accident-involved group admitted use of "tranquilizers" at a rate 4.4 times the frequency in the control group, i.e., drivers not involved in accidents.

iii. Studies of fatally injured drivers. Among studies of drug use in drivers, those that have examined the largest samples and the widest range of pharmacological agents have been conducted in fatally injured victims of accidents (table 10). As in the studies of arrested and nonfatally injured drivers, benzodiazepines and other drugs were often detected in individuals who also had high blood-alcohol concentrations; however, the reports did not always specify whether alcohol or other drugs were also detected. The percentage of benzodiazepine detections ranged from zero, in a study with a small sample size (302), to 10% (338).

A greater incidence of drug detections in fatally injured drivers, who are relatively likely to have been responsible for accidents, than in fatally injured passengers or pedestrians, presumably not at fault, might indicate a contribution of drug use to the risk of accident. Garriott et al. (338) compared fatally injured drivers, passengers, and pedestrians; benzodiazepines were detected in blood of 10% of the drivers, but in only 5% of the passengers and pedestrians. In contrast, Cimbura et al. (170) found no difference in the incidence of benzodiazepine detection in blood from fatally injured drivers and pedestrians. Woodhouse (1171, 1170) examined drugs detected in the blood, urine, or bile of fatally injured drivers and whether those drivers were found to be at fault in the accident. Alcohol was the only drug that was significantly over-involved in fatalities of drivers at fault; however, sufficient data were not available to conduct this type of analysis for subjects positive for tranquilizers.

Two case-controlled studies examined blood or urine samples from living drivers travelling at times and places where fatal automobile accidents had occurred. In one (365), random samples of 501 and 523 living drivers from two communities were compared with fatally injured drivers described in a previous study (1170). Only 21 and 23 of the randomly sampled living drivers from the two samples were determined to have evidence of any drug in blood or urine samples. The incidence of use of all drugs among drivers involved in fatal accidents was about 4 times higher than that in living drivers. Diazepam was confirmed in blood or urine by gas chromatography 3 times more often in fatalities (0.6%) than in control drivers (0.2%). Chlordiazepoxide was confirmed in 0.8% of the fatalities but in none of the control drivers. In this study, the controls included only male drivers, whereas the fatally injured drivers were of both sexes. Since epidemiological data indicate a higher prevalence of benzodiazepine use among women than among men, the conclusions from this study remain tentative.

Blackburn and Woodhouse (84) conducted another

TABLE 9

Studies of nonfatally injured automobile accident victims

References	Geographical area	Dates of survey	Method of detecting drugs	Subject type	No.	Benzodiazepine positive (% of N)			Notes
						(a) EtOH negative	(b) EtOH positive	Sum of (a) & (b)	
Berg et al., 1971 (62)	U.S.A.	1971	Blood	Drivers					
				Accident involved	24	0	0	0	Not case-controlled. Small number of subjects.
				Accident uninvolved	54	0	0	0	
Jick et al., 1981 (531)	U.S.A.	1977–8	Prescription records	Drivers at fault	93			7.0	Examined prescription records for diazepam or flurazepam only.
				Passengers	66			8.0	
				Others	85			6.0	
				Total	244			7.0	
Terhune and Fell, 1982 (1083)	U.S.A.	1979–80	Blood	Drivers	497	5.0	2.4	7.4	Benzodiazepine anxiolytics only. Three samples (0.6%) were positive for hypnotic and one (0.2%) for anticonvulsant benzodiazepines.
Sabey, 1978 (956)	England	1965–74	Interview	Drivers					
				Accident involved	1216			2.1	"Tranquilizers" (undefined) were reported 4.4 times more frequently in the accident-involved group.
				Controls	2075			0.5	
Skegg et al., 1979 (1016)	England	1974–6	Medical records	Drivers	57			8.8	Relative risk of accident with minor tranquilizer use was 4.9.
				Matched controls	1425			2.3	
Ferrara et al., 1980* (289)	Italy		Blood, urine	Drivers	1000	2.8	5.9	8.7	Most in therapeutic range.
Bo et al., 1975 (94)	Norway	1973	Blood	Drivers					
				Accident involved	74	9.5	10.8	20.3	Five accident-involved subjects had concentrations above the therapeutic range. One of these was EtOH positive. Not case controlled.
				Accident uninvolved	204	2.0	0	2.0	
Setekleiv et al., 1980 (1001)	Norway	1978–9	Blood	Auto driver	22	9.1	4.6	13.7	
				Motorcyclist	19	0	5.3	5.3	
				Cyclist	10	0	20.0	20.0	
				Passenger	9	11.1	?		
				Pedestrian	17	0	?		
Honkanen et al., 1980 (489)	Finland	1977	Blood	Drivers					Case-controlled study.
				Accident involved	201			5.0	
				Accident uninvolved	325			2.2	
Missen et al., 1978 (771)	New Zealand	1978	?	?	?	0.3	1.7	2.0	Only tested for diazepam.

* Date of publication; survey date not provided.

TABLE 10

Studies of fatally injured automobile accident victims

References	Geographical area	Dates of survey	Method of detecting drugs	Subject type	No.	Benzodiazepine positive (% of N)			Notes
						(a) EtOH negative	(b) EtOH positive	Sum of (a) & (b)	
Fisher, 1973 (302)	U.S.A.	1969–70	?	Drivers	27	0	0	0	Small number of subjects.
				Passengers	13				
Woodhouse, 1975 (1171)	U.S.A.	1971–3	Blood, urine, bile	Drivers	710			0.4	Alcohol was the only drug that was significantly over-involved in those at fault.
Glauz and Blackburn, 1975 (365)	U.S.A.	1971–3	Blood, urine	Dead drivers	503			1.4	Case-controlled study.
				Living drivers	1,024			0.2	
Bastos and Galante, 1976 (51)	U.S.A.	1974	Blood, bile, brain, urine, liver	Drivers	171			4.7	All tranquilizers grouped, including phenothiazines and antidepressants. Diazepam was typically found at therapeutic levels.
				Pedestrians	254			5.6	
				Passengers	84			3.6	
								3.5	
Blackburn and Woodhouse, 1977 (84)	U.S.A.	1974–75	Blood, urine	Dead drivers	508			0.4	Case-controlled study. Data from males only.
				Living drivers	745			0.4	
Garriott et al., 1977 (338)	U.S.A.	1974–5	Blood, urine	Drivers	207			10	
				Passengers/pedestrians	70			5	
				Total	277			8	
Garriott et al., 1986 (337)	U.S.A.	1985	Blood, urine	Drivers and motorcyclists	122			4	Subjects less than 50 yr old.
Williams et al., 1985 (1145)	U.S.A.	1982–3	Blood	Male drivers (age, 15–34 yr)	440			4	Diazepam (at therapeutic levels in 17 of the total 19 cases).
Cimbura et al., 1982 (170)	Canada	1978–9	Blood, urine, vitreous humor, stomach content, liver	Drivers	401			3	44% of diazepam positives were also EtOH positive. 38% were positive for other drugs.
				Pedestrians	83			5	
				Total	484			4	
Krantz and Wannerberg, 1981 (610)	Sweden	1977–8	Blood, urine, stomach content, liver	Drivers	122	2.5	0.8		Survivors of up to 10 h included. In 1.6% of drivers only benzodiazepines were detected.
				Passengers	55	5.5	0		
Vine and Watson, 1983 (1117)	Australia	1983*	Blood	Drivers	425	1.8	2.1	4.0	
Missen et al., 1978 (771)	New Zealand	1974–77	Blood		370	0.8	0.8	1.6	
Missen et al., 1978 (770)	New Zealand	1977–78	Blood	Drivers, motorcyclists, pedestrians	302			1.0	

* Date of publication; survey date not provided.

case-controlled study of drug use in which all controls were male and the fatally injured drivers were of both sexes. This study showed about a 2-fold higher rate of drug use among fatalities than among control drivers. The rate of benzodiazepine detection was too low for meaningful comparisons between the cases and controls. Tranquilizers as a class (including meprobamate and phenothiazines) were detected no more frequently in male fatalities than in control male drivers. These investigators conducted a culpability analysis of the accident reports pertaining to the fatally injured cases. Interestingly, culpability was not related to drug use; this finding suggests that drivers using these drugs are not more likely to cause accidents than to become involved in accidents caused by other drivers.

2. Effects on the risk of other types of accidents. There are few studies of the effects of benzodiazepines on the risk of accidents not involving automobiles. One study (1211) examined the frequency of drug use by U.S. Air Force pilots involved in aircraft accidents. Evidence of any kind, such as prescription containers found on the body as well as "known" ingestion of drugs, was used as evidence of drug involvement in the accident. Between 1962 and 1973, benzodiazepines were implicated in less than 0.1% of these accidents.

Setekleiv et al. (1001) found evidence of benzodiazepines in blood samples from 12.2% of industrial accident victims admitted to a hospital in Norway; half of these victims had also consumed alcohol. In a questionnaire survey, Proctor (895) found no difference in accident rates of subjects who reported having used diazepam and those that reported no use of medication in the prior 6 mo.

Studies of toxicological findings from body fluids of coroners' cases have indicated the incidences of different types of drugs detected. For example, Dinovo et al. (236) found evidence of benzodiazepine use in 5% of all drug-related or drug-involved deaths from nine major cities in the U.S. during the period from 1972 to 1974. In the absence of an appropriate reference group for comparison, these statistics are not readily interpretable.

Other studies have compared the incidences of drugs detected in accident victims with victims of other types of deaths. Kelly et al. (573) found the incidence of benzodiazepine detection in blood to range from 0.2 to 3.7% in different types of deaths. The highest percentage was from natural deaths, whereas the lowest percentage was in deaths of undetermined cause. Benzodiazepines were detected in 0.4 and 0.7% of vehicular and nonvehicular accidents, respectively. The drugs were detected in 0.5 and 1.1% of homicides and suicides, respectively. In less than 5% of the positives were the drugs detected at greater than therapeutic levels. Similarly, Norton et al. (816) found a greater incidence of diazepam detections in blood of suicide (16%) than of homicide (4%) victims. The highest incidence, however, was detected in natural deaths (22%); this was twice the incidence detected in accident victims.

Elderly patients are frequently prescribed benzodiazepines and also suffer from accidents associated with falls. Kramer and Schoen (608) found no difference with respect to flurazepam use in a group of patients that fell and those that did not fall while hospitalized. However, in patients over 70 yr of age, 70% of those who experienced falls had received prescriptions for flurazepam, while only 19% of patients who did not fall had received such prescriptions. Hale et al. (423) interviewed elderly patients with reference to incidence of signs and symptoms such as dizziness, fainting, blackouts and falls, and bone fractures. Subjects taking tranquilizers (benzodiazepines and meprobamate) suffered from all signs and symptoms except bone fractures significantly more frequently than subjects not taking such medication.

In summary, these studies suggest that benzodiazepines may contribute to a higher risk of accidents under specific conditions. The elderly may be particularly at risk due to the greater sensitivity of this population to the pharmacological effects of these agents. The high rate of detection of benzodiazepines in body fluids of those dying of natural causes is not surprising, considering that these individuals represent a group that is older and more likely to be receiving medication for a variety of medical problems. Additionally, the suicide victims are more likely to have sought medical treatment for their psychiatric conditions (816). The rate of detection of benzodiazepines among accident victims lies between that for natural deaths and the lowest incidences determined. However, reference groups similar to those used in case-controlled vehicular accident studies are necessary in order to adequately interpret studies of benzodiazepine involvement in nonvehicular accidents.

3. Summary and discussion. Epidemiological studies of arrested, nonfatally injured, and fatally injured drivers (excluding studies of subjects selected because drug use was suspected) have found frequencies of benzodiazepine use ranging from near zero to 20%. The frequencies of benzodiazepine use in drivers arrested for driving while intoxicated were generally lower than in nonfatally and fatally injured drivers. The few studies that have attempted comparisons with the general population or with some other reference group have not consistently demonstrated that benzodiazepine users are overrepresented in the populations of arrested drivers or of drivers involved in fatal or nonfatal traffic accidents. Thus, although epidemiological studies have indicated that some proportion of the accident-involved population uses benzodiazepines, these studies have not provided a clear indication as to whether, or to what extent, benzodiazepines may contribute to the risk of automobile accidents.

Laboratory studies complement epidemiological studies by directly examining the effects of drugs on behavior. Experimental studies of both simulated driving and actual driving behavior have indicated that single or repeated therapeutic doses of most of the benzodiazepines that have been tested may adversely affect various parameters of performance in normal subjects. While stud-

ies of driving-related behaviors can provide the best approach for determining the specific behavioral processes that are altered by drugs, these studies have not demonstrated any predictive utility for driving behavior outside the laboratory.

E. Effects on Social Behaviors

1. Effects on well-being and interpersonal relations. A study reported by Caplan et al. (153, 154) is of particular interest because of its unique design, rigorous controls, sophisticated use of statistical analytic techniques, and because it was the first investigation of an extremely broad array of social behavioral effects of the use of benzodiazepine anxiolytics. The study population was identified on the basis of the records of a random sample of pharmacies in the Detroit area, stratified to represent a broad range of neighborhoods with regard to sociodemographic characteristics. The 675 subjects included adults who had filled a prescription for diazepam within the 6 wk prior to recruitment and a control group of adults who had filled a prescription for another, nonpsychoactive medication in the same period. In addition, each diazepam user was asked to nominate a "significant other" from his or her personal life (e.g., a spouse) and, if employed, from his or her work life; these significant others also served as study subjects. In a panel survey design, each subject was interviewed 4 times at intervals of 6 wk.

The group of users was similar in most respects to anxiolytic users identified in random-sample surveys of the U.S. population (as described below in section V E 2, pages 346 to 348); however, possibly because these subjects were selected because they had recently filled a diazepam prescription, they included a higher proportion of daily or almost-daily users (48% at the first interview).

Study measures were standard instruments drawn from the literature (including the Hopkins Symptom Checklist for measurement of affective states), or were developed and pretested for reliability. Potential outcome variables included subjects' sense of control; providing and eliciting social support; affective states (anxiety, depression, anger); perceived quality of life (satisfaction); use of caffeine, alcohol, and other psychoactive drugs; ability to manage emotions; ability to perform responsible roles in work and personal life; as well as the well-being of significant others. The study reports (same refs. as above) carefully described the efforts made to ensure the reliability of the instruments and to test the reliability of interview data.

Diazepam users who used the medication daily were significantly less likely than nonusers to consume alcohol; also, diazepam users drank less alcohol during periods when they were taking diazepam than when they were not. Diazepam users were more likely than nonusers to smoke cigarettes, but did not differ from nonusers with respect to use of caffeine or illicit drugs; use of illicit drugs was very infrequent among all subjects.

A main finding of the study, on the basis of correlational, lagged analyses, change score analyses, and structural modeling techniques, was that there was no evidence of either harmful or beneficial social effects of diazepam use for all users or for various subgroups of users. Analysis of covariance, controlling for the higher levels of perceived stress and poorer health among users compared with nonusers, was applied to data for daily users, new users, and highly anxious nonusers; this analysis also found no evidence of any long-term effects of diazepam use on performance, affective states, the well-being of significant others in the subjects' personal lives, and many other variables.

The investigators cited others' hypotheses that the use of benzodiazepine anxiolytics may dull users' sense of the external environment and may numb their emotional responsiveness. They found that this study did not support these hypotheses, since there was no difference between users and nonusers with respect to the relations between social stresses (e.g., role conflict) and emotions (e.g., anger).

Proctor (895) studied the effects of diazepam use on occupational performance and absenteeism (as well as accident rates, discussed previously) among employees of three large manufacturers of fine wood furniture. Drug use was determined by means of questionnaires sent to the subjects, who were divided into categories according to the types of medications they had used in the prior 6 mo, including diazepam, other psychoactive drugs, nonpsychoactive drugs, and no drugs. The companies' personnel departments provided data on absenteeism and supervisors' ratings of work performance. There was no difference in mean performance ratings of subjects who reported having used diazepam and those that reported no use of medication in the prior 6 mo. Absenteeism was greater for the group reporting use of diazepam than for those who had used no medication, but not different from those reporting use of some medication.

2. Effects on aggression. It has been debated for some time whether administration of benzodiazepines leads to increases or decreases in aggressive behavior. A number of case reports of individuals have suggested that hostility, irritability, and, in some cases, overt aggression have resulted from benzodiazepine ingestion (e.g., refs. 1080, 669, 511, 1213, and 1214). Since benzodiazepines were originally reported to produce "taming" in normally aggressive monkeys (903), these increases in hostility were considered evidence of idiosyncratic "paradoxical reactions" (1213). A series of studies from one laboratory in the late 1960s and early 1970s suggested that increased hostility was a fairly common result of chronic benzodiazepine ingestion. Gardos et al. (333) studied three groups of healthy male volunteers who had been screened for their anxiety levels on the Taylor Manifest Anxiety

Scale (TMAS). Each group consisted of 15 subjects with either high, medium, or low anxiety. Subjects in each group were given either placebo, oxazepam (45 mg/day), or chlordiazepoxide (30 mg/day) for 1 wk; twice during the week they were evaluated on several questionnaires to ascertain current levels of anxiety and current levels of hostility. As had been found in earlier studies (234, 49), the active medication produced increased anxiety in those with low anxiety scores in the original tests and decreased anxiety in those with high anxiety scores on the original tests. Neither placebo nor oxazepam produced changes in hostility as measured by the Buss-Durkee Hostility Index (BDHI). However, scores on the BDHI and on the Gottschalk-Glesser Hostility Scale were significantly elevated by chlordiazepoxide in subjects who had shown high anxiety levels.

DiMascio et al. (235), in a similar study, found increased BDHI scores following 1 wk of 15 mg/day of chlordiazepoxide administration to subjects with either low or high anxiety scores. The subscales of verbal hostility, direct hostility, and motoric hostility were particularly increased.

Salzman et al. (963) performed a double-blind study of the effects of 1 or 2 wk of 30 mg/day of chlordiazepoxide administration to subjects with low anxiety. Subjects were told that the drug would produce a calming effect and would decrease hostility. Some subjects were told this after receiving the drug for 1 wk and prior to receiving the drug for another week. Other subjects were told this prior to 1 wk of placebo administration. Whereas the drug alone did not significantly increase hostility scores, the "expectancy" of a calming effect resulted in significantly increased hostility scores for subjects receiving either drug or placebo. This effect of "instructions" was unexpected and unexplained. The lack of drug-induced increase in hostility measures was attributed to the fact that the subjects had low levels of anxiety, since previous studies (333) had indicated that low-anxious subjects did not develop hostility under chlordiazepoxide administration.

The effects of 30 mg/day of chlordiazepoxide on hostility in a small group setting was tested by Salzman et al. (964). Two groups of 24 individuals each were studied; one group received drug and the other received placebo. Each group of 24 was divided into smaller groups of 3 subjects per group. Each subject was tested on the BDHI and the TMAS (*a*) at the beginning of the experiment, (*b*) after spending 10 min in the group trying to reach a consensus on a story about a picture from the Thematic Apperception Test, (*c*) after 1 wk of drug or placebo administration, (*d*) after another 10 min of discussion in the group after chronic drug or placebo administration, and (*e*) after being told that the group's performance on developing a story was "inadequate" and had to be repeated. In addition, each subject was requested to judge the hostility of other members of his group.

The results indicated that neither total scores on the BDHI nor subject ratings were changed by drug administration in the subjects as a whole. There was, however, a significant change in the assaultive subfactors of the BDHI in subjects receiving chlordiazepoxide, and, if only subjects showing high anxiety levels on the TMAS test were considered, both total and assaultive scores were increased by chlordiazepoxide. There was no further increase in these scores following introduction of the "frustrating" stimulus of being told performance was "inadequate." However, the ratings of hostility of fellow group members were increased following the frustrating stimulus in groups receiving chlordiazepoxide. One chlordiazepoxide subject became so angry after being told the performance was "inadequate" that he left the experiment.

Kochansky et al. (590) administered 45 mg/day of oxazepam, 30 mg/day of chlordiazepoxide, or placebo to subjects with moderate to high anxiety as measured on the TMAS. Scores on the BDHI were compared before and after 1 wk of drug or placebo administration. Two-thirds of the subjects taking chlordiazepoxide showed scores indicative of increased hostility, whereas one-half of those taking oxazepam and one-third of those on placebo showed similar changes in hostility. The changes in mean scores on the BDHI were not significantly altered by drug administration, but the change in the subscale of verbal hostility was increased significantly in subjects receiving chlordiazepoxide administration compared to those receiving oxazepam. Interestingly, subjects who received oxazepam had higher verbal hostility scores prior to drug administration than did those who received chlordiazepoxide or placebo.

Although most of these studies either reported or suggested that hostility increased in subjects with high measured levels of anxiety, an opposite finding was reported by Wilkinson (1142), who used an actual behavioral measure of aggression in her studies of the effects of diazepam. Subjects were told that the experiment was a test of relative reaction times. They had to remove their finger from a button with the onset of a stimulus light, and, if they were slower than an "opponent," they would be shocked. The level of shock was said to be set by the "opponent," and they, in turn, could set the level of shock that the "opponent" would receive. In fact, there was no "opponent," and the subjects received shock on 50% of the trials, at preprogrammed levels that became higher as the session progressed. Subjects were selected, on the basis of their scores on a trait-anxiety measure, as having low, intermediate, or high anxiety levels. Aggression, as measured by the level of shock selected for the opponent, was increased by the administration of 10 mg of diazepam 60 min earlier, as compared to placebo. This occurred under conditions of low provocation, i.e., when the level of shock being received by the subject was low, and was most pronounced in subjects with low

anxiety scores. When the provocation was increased by increasing the level of shock to the subjects, those who had received diazepam responded by assigning higher levels of shock to their "opponent" than did subjects receiving placebo. This occurred regardless of the anxiety level of the subjects. Thus, in contrast to other studies, it appeared that acute administration of a relatively low dose of diazepam could result in increased aggressive behavior, particularly in subjects with low anxiety.

Griffiths et al. (394) studied the effects of 5 consecutive days of administration of 50 or 100 mg/day of diazepam, or 200 or 400 mg/day of pentobarbital, on hostility in 12 male sedative-drug abusers. A 10- to 14-day "washout" period followed each 5-day period of active medication. The subjects were in a group setting on a research ward, but each subject was evaluated singly in this particular study; other subjects on the ward were participating in other experiments. The drugs were administered at 11 a.m., and at 1, 3, and 5 p.m., the subjects took the POMS questionnaire and were rated by the ward staff on mood, social interaction, and hostility. There was a clear increase in hostility, as rated by the ward staff, across the first 3 to 4 days of diazepam administration for each of the subjects. Interestingly, the self-rating inventory (POMS) showed no change. Similar changes were not observed in subjects taking pentobarbital.

The authors of this report (394) indicated that the increases in hostility were subtle in nature, but were not idiosyncratic, since they were observed in each of the subjects. The fact that such increases were not observed with pentobarbital raised the possibility that drugs that are more quickly metabolized, with little accumulation over time, may be less likely to produce hostility. This could account for the lack of effect reported with oxazepam by earlier investigators. Interestingly, in early studies of pentobarbital dependence in human subjects, Isbell (515) reported profound increases in fighting behavior among subjects who were taking as much as 1.3 to 1.8 g of secobarbital or pentobarbital daily. This supports the idea that maintained high levels of sedative drugs are necessary to produce increases in hostile behavior. It also suggests that the effects may not be limited to long-acting benzodiazepines, but may occur with shorter-acting benzodiazepines or other sedatives if they are given frequently and in sufficiently high doses.

Downing and Rickels (246) contended that studies of the kind described above were conducted in inappropriate subject populations. These investigators measured changes in scores on the BDHI and on the Hostility Conflict Scale, which is designed to measure guilt about hostile feelings, in 80 anxious neurotic outpatients. The patients were given 30 to 40 mg of chlordiazepoxide daily for 4 wk. A significantly increased verbal hostility score was found only in patients who initially had low hostility conflict scores; those with high hostility conflict scores showed significant decreases in hostility following chlordiazepoxide administration. Other subscales, such as those measuring irritability and resentment, actually showed slight decreases by chlordiazepoxide. Downing and Rickels concluded that, in the patient population that was likely to receive prescriptions for benzodiazepines, hostility is more likely to be decreased than increased by these drugs.

In summary, experimental and case-study materials on the development of hostility in subjects taking benzodiazepines present conflicting information. It appears that benzodiazepines can increase hostility in a nonclinical population, but it is not clear whether this occurs selectively in subjects with low anxiety or in subjects with high anxiety, whether it requires chronic administration, or can occur with acute administration. It is possible that the results obtained are strongly determined by the way hostility is measured. Different results appear to result from pencil-and-paper tests of hostility, observer-rating tests of hostility, and behavioral tests of hostility. Whether increased hostility is a clinically significant problem will probably remain uncertain until there is better understanding of the variables that contribute to the results obtained thus far. Whatever conclusion is ultimately drawn about benzodiazepine-induced hostility in the typical patient population, acute ingestion of high doses of benzodiazepines may be capable of producing much more profound "rage" reactions in occasional individuals.

F. Summary and Discussion

Research has identified a number of behavioral changes that can occur in association with administration of benzodiazepines, ranging from subtle effects on psychomotor performance as measured under laboratory conditions, to more global effects on social interactions. Studies of patients for whom benzodiazepines have been prescribed have found no effects of use of these drugs on subjective well-being, on interpersonal relations, or on work performance. Most of the effects demonstrated in the laboratory appear to be greatest following initial administration of acute doses of the drugs and subside or disappear with repeated administration.

A variety of behavioral performances are affected by benzodiazepines. Effects observed include seemingly simple "coordination" tasks, as well as more complex tasks such as performing arithmetic problems without the benefit of paper and pencil. These effects are seen in both normal and anxious subjects; however, low doses of benzodiazepines administered as hypnotics to insomniacs appear less likely to affect performance when measured on the following morning. In any case, there is no clear indication of the predictive utility of the results of these psychomotor-performance tests for performances outside the laboratory.

The effects of benzodiazepines on recall are demonstrated quite reliably and may be more likely to alter the

behavior of patient populations receiving these drugs. Acute administration of therapeutic doses clearly impairs delayed recall. Although there is little relevant evidence, it has been suggested that tolerance may not develop to this amnestic effect with chronic administration. Elderly subjects are generally more susceptible to the behavioral effects of benzodiazepines, a susceptibility that may be especially important with respect to these effects on recall. There is clearly a need for further investigation of these suggestions.

A great deal of attention has been focused on experimental research into the effects of benzodiazepines on driving performance and on the possibility that use of these drugs may increase the risk of traffic accidents. Performances of normal subjects in simulated driving tasks were affected by several of the benzodiazepines administered in single therapeutic doses. Diazepam has been studied frequently and has been found to increase errors in maintaining lane position or tracking. Other effects of diazepam have included neglecting instructions, increased speed, decreased reaction times, inability to maintain heading after simulated wind gusts, and increased frequency of collisions. Other benzodiazepines, including chlordiazepoxide, lormetazepam, and flurazepam, have been shown to adversely affect tracking and reaction times in driving simulators. Actual driving performance of normal subjects was affected by several of the benzodiazepines. Single doses of diazepam, chlordiazepoxide, clobazam, and flurazepam had effects on some parameters of driving with inconsistent effects on performances in other tests. Some studies have found no effects of therapeutic doses of other benzodiazepines, although these other drugs have been studied much less frequently.

Driving simulations attempt to model complex behaviors, and in doing so these tests relinquish simplicity for face validity; while such complexity may be required in order reliably to model extralaboratory behaviors, it is often difficult in these experiments to isolate or identify the specific behavioral process that is affected by the drugs tested. Studies of actual driving behavior impose conditions that are often significantly different from the circumstances under which individuals normally drive; a subject may be more likely to exhibit performance impairment in the laboratory than while driving in actual traffic, since the potential consequences of impairment in laboratory situations are less severe. Thus, while these types of studies are of use in determining which drugs, at which doses, will affect actual driving, they may overestimate the extent to which actual driving might be impaired by use of benzodiazepines.

Although epidemiological studies have indicated that a proportion of the accident-involved population uses benzodiazepines, whether the use of benzodiazepines increases the risk of accidents remains unclear. There are several reasons why these studies are inconclusive. First, the relationship between levels of drugs in various body fluids and degree of behavioral impairment has not been clearly established; thus an association of drug use and accidents cannot be regarded as causal. Second, the incidence of detection of a specific drug in a series of accidents does not necessarily indicate whether or to what extent this drug has contributed to the likelihood of accident, since other drugs, particularly alcohol, may have also been present.

Further, it is unlikely that epidemiological research can provide more definitive evidence about this question, because the most satisfactory epidemiological studies of this kind, namely those using case-control designs, are probably not feasible. In case-controlled studies, living control drivers are sampled at the same times and places as the drivers that are involved in accidents. In the few case-controlled studies that have been conducted, the number of living drivers that has been positive for drugs has been exceedingly low, rendering assessments of risk difficult. These studies, however, have not controlled for all relevant variables. More extensively controlled studies would require that benzodiazepine-using drivers be matched with control subjects who have comparable medical and psychiatric conditions. In addition, as other epidemiological research indicates, the majority of drivers (or any other such population subgroup) using benzodiazepines at any given moment are those who use these drugs regularly for relatively long periods of time. As indicated by laboratory studies of the effects of such chronic administration of benzodiazepines, the performance of these drivers is unlikely to be impaired by their drug use. Drivers who are more likely to be at increased risk of accidents are new users, or those who may take these drugs on an infrequent, occasional basis. To take these factors into account would necessitate sampling a prohibitively large number of drivers in order to have a number of drug-positive subjects sufficient for predictions and assessment of risk.

V. Epidemiology of Benzodiazepine Use and Misuse

A. Introduction

1. Problems of context. The voluminous literature on misuse of the benzodiazepines tends to dwell on the countless details of the context of misuse per se. In order to arrive at a broader perspective, in which the significance of this misuse might be interpreted relative to the clinical uses of these medications, the following section will consider the evidence regarding the actual use of the benzodiazepines, including statistics on sales of these drugs as well as findings of research applying traditional epidemiological measures to the study of their use and misuse.

Assessment of the abuse liability of the benzodiazepines in the context of what is known about how these medications are actually used might also provide valuable

benchmarks for comparative assessment of other substances, for which the characteristics of use have not been so well documented. It is hoped that this review will serve to provoke similar considerations with respect to other drug classes, e.g., narcotic analgesics and CNS stimulants.

While there appears to be a vast literature on the use of benzodiazepines, and of psychotropic drugs in general, the great majority of these studies have focused simply on the extent of use of these agents in various populations, and they have presented such statistics as if they were meaningful in themselves. This emphasis raises a number of questions regarding the appropriate context in which these data might be interpreted.

In general, statistics on the extent of use of benzodiazepines, or of any other medications, must be interpreted cautiously, since there is a much broader context governing the utilization of drugs within and across populations. Use of prescribed medications is a function of a wide array of factors, including factors dictating availability, such as national and international regulation, and pharmaceutical marketing practices and competition; demographic, socioeconomic, and cultural characteristics of populations for whom the drugs are available; professional variables relating to the populations' physicians; economic factors affecting individuals' ability to fill prescriptions; etc. (898). These factors vary in their interaction and net influence at different times and in different places.

Secondly, the frequent emphasis on the simple extent of use of the benzodiazepines appears to reflect a common perception that the widespread use of anxiolytics and hypnotics is a new phenomenon, requiring urgent attention. It seems remarkable that this perception has never been seriously questioned. Section V B below offers an historical perspective on the extent of use of anxiolytic and sedative drugs in previous pharmacological periods.

Beyond these considerations, data on the extent of use of the benzodiazepines appear meaningful only when they are presented in a context, or can reasonably be viewed in a context, such that they can shed light on specific questions regarding the significance of this drug use. For the purposes of this review, these data will be considered chiefly as they relate to the following three primary focuses:

(*a*) the appropriateness of actual use of the benzodiazepines, that is, the extent to which the benzodiazepines are prescribed and consumed for conditions for which their use is generally considered safe and effective versus the extent to which they are used for other conditions or in the absence of specific psychiatric or medical objectives;

(*b*) the patterns of actual use of benzodiazepines. The review will consider the available information on patterns of physicians' prescribing for individual patients and the extent to which this information appears relevant to the question of the appropriateness of medical and psychiatric use of these drugs. More importantly, it will consider information on patterns of actual consumption of the benzodiazepines, which bears more directly on their relative liability for abuse and dependence; and

(*c*) any direct or indirect evidence of misuse or dependence in the general population or patient survey data, as well as such evidence from studies focusing specifically on misuse and poisoning.

2. *General limitations of the data.* There is wide geographical variation in the amount of epidemiological information available on the use of psychotropics, as there is generally on the use of all medicines (e.g., ref. 249). The most substantial body of information relates to use in the U.S. There is also considerable information available for the United Kingdom and for some Western European nations. In general, we have only glimpses of use in other countries.

The amount of information available on the use of the different individual benzodiazepine compounds also varies markedly. Obviously data on actual use are limited to those compounds already introduced into medical practice and virtually to those compounds that have been on the market long enough to gain relatively extensive use in various countries.

Another major limitation of the epidemiological data pertains to taxonomic and methodological discrepancies among the studies that have been reported. While some studies have examined use specifically of individual benzodiazepines, or of anxiolytic or hypnotic benzodiazepines as a group, the majority of relevant studies have considered broader pharmacological groups, e.g., "minor tranquilizers" or psychotropics in general. These studies are relevant, even when they do not identify results pertaining specifically to benzodiazepines, because in many instances it is reasonable to suppose that benzodiazepines account for a substantial proportion of the use reflected; and in some instances, depending on the time and place of the study, it is even possible to calculate fairly closely the actual percentage of the reported use accounted for by benzodiazepines. In discussing these studies, we have specified as nearly as possible what drugs or drug groups were represented. Where it was not possible to be more specific, we have used the terminology of the original reports. There is no question that what was intended by terms such as "tranquilizers," "sedatives," or "psychotropics" has varied by region and over time; thus much of the information discussed is most meaningful within the specific contexts of individual studies. Nevertheless, we feel that the data have an overall coherence and consistency that outweigh the risks of misinterpretation introduced by these ambiguities.

A greater problem of incommensurability derives from methodological discrepancies among the available studies. In some studies the measurement of drug use is based on numbers of patients receiving prescriptions or on

patient visits at which prescriptions are issued; in others it is based on numbers of prescriptions for a given population. Within each of these general categories, there is further wide variation in the ways in which investigators arrive at the numerators and denominators used to estimate drug exposure of the study population. Studies also vary in the ways and extent to which they consider such factors as the duration of individual prescriptions, numbers of pills and daily dosages prescribed, and refill patterns.

One significant approach to standardizing the measurement of drug utilization was suggested by the Norwegian Medicinal Depot (Norsk Medisinaldepot), which in 1975 published a list of "defined daily doses" (DDD) of all drugs for systemic use registered at that time in Norway. The DDD was intended to represent "the average maintenance dose when used routinely for the assumed major, or one of the major, indications for the actual drug . . ." (688). This unit of measurement can thus be used to describe the proportion of persons within a population that is exposed to a particular drug in a given period of time; it has most often been used in the form "DDD/1000/day," meaning the number of defined daily doses per 1000 inhabitants per day. Use of the DDD measure was urged as a basis for international comparisons by the Drug Utilization Research Group, an international organization formed under the WHO. While this measure has been applied in a number of studies, it has by no means gained universal acceptance. Data from the great majority of drug use studies remain generally incommensurable.

3. Limitations and organization of the present review. This review does not attempt to sort out the differences resulting from these methodological disparities with respect to the absolute extent of use of benzodiazepines. Some estimates of the extent of use are considered in and of themselves; these are derived from national and cross-national studies which appear unusually reliable because of specific efforts to validate the study measures. Other estimates of the extent of use are considered when these data are presented in the context of either medical need or abuse or dependence within the same population. Beyond these studies, illustrative examples of other research concerned with the extent of use are provided in tables and discussed briefly in the text.

This review is not intended to represent all of the very substantial literature on the use of the benzodiazepines. We have attempted to consider all of the most important publications presenting original data; surely we will have missed some even of these. With regard to the remaining bulk of the literature, the present coverage is best described as representative.

Section V, C to E, focuses, respectively, on prescription sales, i.e., wholesale and retail sales data; surveys of prescribing patterns, considering surveys of both physicians and prescription records; and surveys of consumption, i.e., surveys in which samples of various populations are questioned regarding their use of benzodiazepines (and other drugs). This last category actually provides the information most relevant to the present interests. The sequence of these three sections has been adopted because the consumption data are best interpreted in the context provided by the sales and prescription data.

Section V F considers the use of the benzodiazepines among certain special populations, especially the elderly, who may be particularly susceptible to the pharmacological effects of these medications, including toxic effects.

Section V G reviews evidence pertaining specifically to misuse of benzodiazepines, including data on the prevalence and patterns of misuse and recreational use among the general population and drug-abusing populations, as well as surveys of drug overdose or drug-associated deaths.

Within the sections below, except where the purpose of clarity dictated otherwise, the information available from each category of research is presented in the following geographical order: U.S.; Canada; the United Kingdom; other Western European nations; other European nations; and other countries. Within countries, the information is reviewed in the order of the date when the research was conducted (or the date of publication, when the survey date was unclear).

B. Historical Perspective on Extent of Use

Review of the epidemiological literature on the benzodiazepines suggests that there is a common perception, among many scientists as well as the lay public, that the so-called "psychoactive" drugs have never been so widely used in medicine as they are today. The frequency with which such drugs are prescribed is taken to be a uniquely contemporary phenomenon. This perception has become a fundamental part of the context in which benzodiazepine use is studied and interpreted, and it has led many observers to assume that the benzodiazepines are overprescribed and overused, without considering the prevalence of the problems for which these drugs are typically prescribed.

The epidemiological research reviewed in this article indicates that benzodiazepines are indeed among the most frequently prescribed medications, and that an average of 2% of the adult populations of the countries that have been studied use these drugs daily on a chronic basis. However, a review of some typical prescription surveys from the past century suggests that it is not clear that these current figures represent a new level of use of sedative-hypnotic medications.

Fig. 3 summarizes the relevant data from a number of prescription studies; the studies are described in table 11. These include all of the major prescription audits conducted in the U.S., at least up to 1950, and include tabulations forming the basis for the development and

later revisions of the United States Pharmacopoeia and of the National Formulary (342). It should be noted, however, that few of the early studies are representative of more than a very limited geographical region, and a variety of differences in recording and reporting policies and methods render detailed comparisons of absolute levels extremely difficult or misleading.

Thus, fig. 3 shows the relative proportion of prescriptions accounted for by the categories of drugs that were recommended as sedatives or hypnotics at the time each study was conducted. Since the selection of drug categories represented was to some extent judgmental, wherever possible we have shown the specific drug classes included as well as the totals.

Fig. 3 A displays the earlier data in terms of the frequency with which specific classes of sedative-hypnotic ingredients were prescribed per 10,000 prescriptions written, the customary method of presenting such data at the time. Fig. 3 B displays sedative-hypnotic prescriptions as a percentage of all prescriptions dispensed, as is customary today. The relationship between panels A and B can be roughly gauged by referring to the Mordell study (781), which appears in both panels because it provided rates of occurrences per 10,000 prescriptions written as well as the percentage of all prescriptions dispensed that were for sedatives and hypnotics.

It should also be noted that the data in the figure do not reflect the purposes for which drugs were prescribed. Thus, panel A includes opiates, which were commonly used for sedation, though some of the use shown was, of course, for analgesia; similarly, some of the prescriptions shown in panel B for "minor tranquilizers" were intended for treatment of somatic problems.

As the figure indicates, drugs available for sedation in the earlier periods were from a variety of pharmacological categories and were relatively nonspecific by current standards. Shifts within and among categories occurred as relatively more specific agents became available, and as the risks associated with the older agents were increasingly recognized. However, despite these shifts over time, the figure makes the general point that, since relevant data first became available, drugs used as sedatives and hypnotics have accounted for a substantial and relatively stable proportion of all prescriptions.

Fig. 3 B indicates that, in 1975, i.e., the year in which benzodiazepine sales peaked in the U.S. (505), total minor tranquilizer and hypnotic sales accounted for approximately the same percentage of all prescription sales

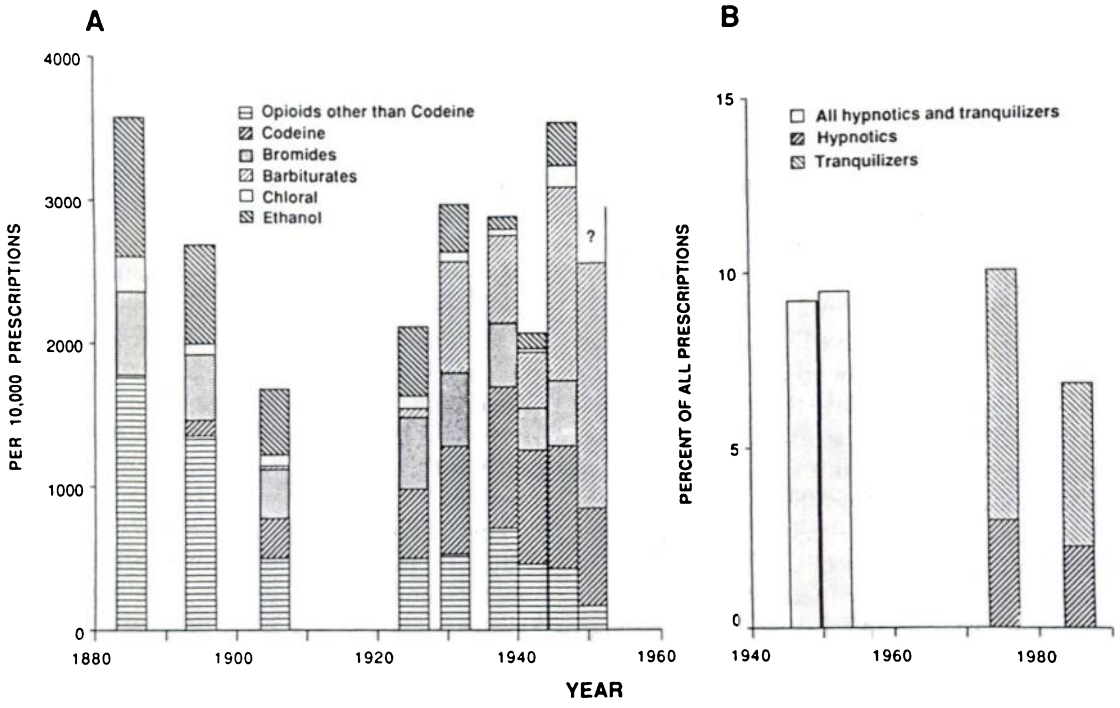

FIG. 3. Frequencies of prescriptions for drugs recommended as sedatives or hypnotics at various dates in the past century in the U.S. Table 11 indicates the studies (and survey dates) from which these frequencies were calculated, except for the two later *bars* in panel *B*, which were based on NPA data (505) for 1975 and 1984. Panel *A* represents frequencies of sedative-hypnotic prescriptions per 10,000 prescriptions written; panel *B* displays sedative-hypnotic prescriptions as the percentage of all prescriptions. The question mark (?) at the *top* of the *bar* representing the data from Raubenheimer (907) indicates that, because of the manner of tabulation, it was not possible to represent the frequency of prescription of bromides or of ethanol for this study. The scale for panel *B* was determined by reference to the Mordell study (781), which is represented in both panels because it provided frequencies of sedative-hypnotic prescriptions both as rates of occurrences per 10,000 prescriptions written and as the percentage of all prescriptions. The figure indicates that, although the categories of medications used for sedation have shifted, these agents have accounted for a substantial and relatively stable proportion of all prescriptions since the earliest relevant records became available.

TABLE 11
Major U.S. prescription audits through the early 1950s

Study	Source of data	Region	Date of survey
Ebert, 1885 (264)	17,734 Rx* from 9 pharmacies; 46,380 occurrences (drugs prescribed); 2.9 ingredients/Rx	IL, chiefly Chicago	c. 1884
Hallberg, 1895 (425)	12,000 Rx from 10 pharmacies; 28,502 occurrences; 2.4 ingredients/Rx	IL	c. 1894
Hallberg and Snow (unpublished†)	117,000 Rx; 215,165 occurrences; 1.8 ingredients/Rx	28 states	1907
Charters, 1927 (165)	17,577 Rx; 40,898 occurrences; 2.3 ingredients/Rx	15 urban centers	c. 1926
Gathercoal, 1933 (342)	121,924 Rx; 257,577 occurrences; 2.1 ingredients/Rx	NY, CA, MD, MO	1931–2
Heine and Lee, 1941 (449)	35,093 Rx from 5 drug stores	Lafayette, IN	1939
Plein and Rising, 1941 (875)	10,715 Rx	"Western state"	c. 1940
Mordell, 1949 (781)	12,668 Rx	186 towns and cities in 39 states	Nov. 1946
Raubenheimer, 1951 (907)	15,480 Rx	New York City	1949
Doyle, 1953 (247)	231,860 Rx	Not stated	c. 1952

* Rx, prescription(s); c., circa.
† Data summarized in Gathercoal (342).

as had sedatives and hypnotics in the bromide-barbiturate era (cf. Mordell from 1949; ref. 781). Sales of minor tranquilizers declined from 1975 to 1981, and then slightly increased to 1984 (e.g., see ref. 57).

Similar findings, at least for the bromide-barbiturate era and the benzodiazepine era, have been reported for the United Kingdom. Surveys of prescriptions subsidized by the National Health Service indicate that sedatives and hypnotics accounted for about 15% of all prescriptions dispensed in England in 1949 and 1951 (260, 363) as well as in 1975 (1152).

This apparent stability in the percentage of all drug sales accounted for by sedatives and hypnotics does not, of course, mean that there has been no change in the volume of actual consumption of these drugs. Data from a variety of sources indicate that there has been "a general increase in drug consumption in all countries over time, whether considered by total or per capita consumption in numbers of prescriptions or expenditure" (900). Nevertheless, interview surveys have shown little or no change in the overall prevalence of use of anxiolytics and sedatives since at least the mid-1960s (see section V E).

These data therefore suggest that the extent of use of sedative and hypnotic medications has remained basically stable, relative to all drug use, since the earliest relevant records were made; and that the prevalence of use has not changed substantially at least in several decades. This stability has survived considerable social, economic, and medical changes. It seems reasonable to assume that it is a reflection of the psychiatric morbidity that motivates use of these drugs, and which is generally estimated to affect about 15 to 20% of virtually every population; the stability of this morbidity over time and across countries has been extensively documented (e.g., refs. 989, 1033, and 241).

Thus, the relatively widespread use of drugs that depress the CNS is not a new phenomenon; the chief difference from period to period is in the specific drugs or drug categories used for treatment of anxiety and sleep disorders. Neither is it a new phenomenon that people noticing momentary shifts in use of psychoactive drugs believe that they are witnessing an alarming departure from previous norms. In the United Kingdom, production of barbiturates doubled between 1938 and 1946, doubled again by 1950, and then levelled off for the remainder of the decade (363). In the midst of the rapid increases in barbiturate consumption, Dunlop (260) reported a prescription survey, and wrote: "It is a significant commentary on present-day conditions that hypnotics and sedatives should form far the largest single group (15%) of all drugs prescribed." Likewise, between 1965 and 1970, as use of the barbiturates declined, Parish (848) noted that "the phenomenal increase in the prescribing of the

hypnotics [nitrazepam and methaqualone] and the minor tranquilizers [chlordiazepoxide and diazepam] is difficult to explain." Trethowan (1089) described this period of change as indicative of "the relentless march of the psychotropic drug juggernaut."

The fact that the relative proportion of prescriptions written for sedatives and hypnotics has remained essentially stable over time does not indicate that this use is necessarily appropriate. However, many of those who have argued that use of these agents is excessive have based their arguments implicitly or explicitly on a perceived increase in psychoactive use coincident with the advent of the benzodiazepines. This perception has tended to prejudge the question of the appropriateness of the current use of benzodiazepines. This question can reasonably be addressed only in the context of the prevalence and consequences of the illnesses for which these drugs are prescribed, and of their safety and efficacy relative to those of other drugs available to treat these problems.

C. Prescription Sales

Prescription sales data provide rough estimates of the level of consumption of benzodiazepines as a group and of individual benzodiazepines. Wholesale data are of some interest, in that they provide some indication of the proportion of the drug consumption of some national populations that is accounted for by benzodiazepines; these data have also presented a practical basis for comparison of benzodiazepine consumption across a number of European countries. Both wholesale and retail sales data portray changes in levels of use over time, within and across countries, providing an interesting history of the typical "life cycle" of these agents in areas where they are marketed. International retail sales data afford a perspective on the variation in popularity of individual benzodiazepines, relative to one another and to other drugs prescribed for anxiety and insomnia, in different parts of the world. Such data on the comparative licit availability of individual benzodiazepines in different areas may also serve as a reference point in evaluations of the drugs observed in illicit traffic. These kinds of global comparisons represent the chief value of prescription sales data for the purposes of this review; sales data provide only very crude estimates of actual consumption and shed no light in themselves on the immediate circumstances of benzodiazepine use.

1. Studies of wholesale data. In 1985 psychotherapeutic agents accounted for 7.5% of all drugstore and hospital purchases of ethical drugs in the United States. Benzodiazepine tranquilizers accounted for 48.2% of all purchases of psychotherapeutics or 3.6% of all pharmacy and hospital purchases (506, 507).

Estimates of the use of benzodiazepines in Norway, Finland, Iceland, and Sweden have been made on the basis of wholesale sales data, recalculated in terms of DDD/1000/day (see page 321). Between 1966 and 1977, sedatives (including hypnotics, tranquilizers, and intravenous anesthetics) were the most frequently sold of all psychotropics in Finland, Norway, and Sweden (457). Wholesale data for these countries during this period reflected a shift in consumption from barbiturates to nonbarbiturates, especially diazepam and nitrazepam (457, 401). Between 1971 and 1976, hypnotic sales were at similar levels in Iceland, Sweden, and Norway, but were lower in Finland; minor tranquilizer sales were at similar levels in Finland, Norway, and Sweden, but were at double that level in Iceland, especially for benzodiazepine tranquilizers (401).

Between 1966 and 1977, sales of minor tranquilizers steadily increased in Finland; increased up to 1970, then levelled off in Norway; and decreased after 1969 in Sweden. Sales of hypnotics steadily decreased in Finland, steadily increased in Norway, and in Sweden slightly decreased in the latter half of this period. In 1977, diazepam and nitrazepam together accounted for 20% (or about 26 DDD/1000/day) of psychotropic sales in Finland; 25% (or 37 DDD/1000/day) in Sweden; and 35% (or 42 DDD/1000/day) in Norway (457).

Between 1970 and 1980, while sales of barbiturates and of some nonbarbiturate and nonbenzodiazepine sedative-hypnotics substantially decreased, sales of benzodiazepines (flurazepam, nitrazepam, and flunitrazepam) increased; this increase between 1974 and 1980 was from about 14 to about 25 DDD/1000/day. According to Joldal and Halvorsen (533), during the 1970s sales of tranquil-

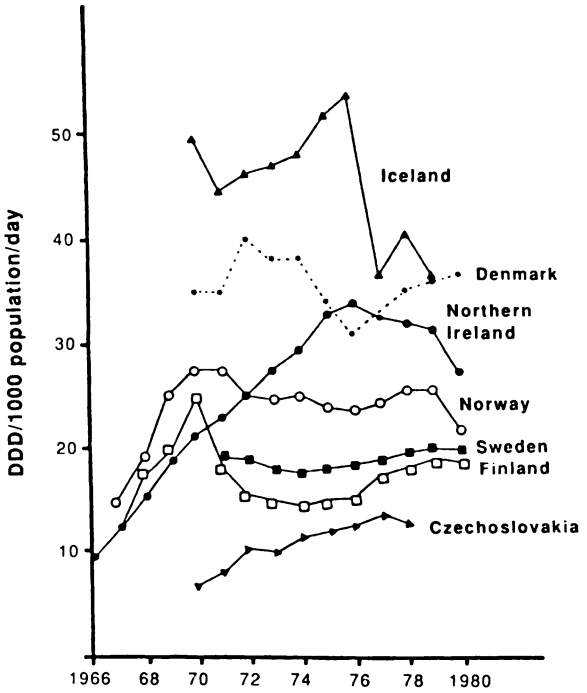

FIG. 4. Benzodiazepine tranquilizer use in various European countries for 1966–1980, as calculated in DDD/1000/day. Data for Czechoslovakia, Finland, Iceland, Norway, Sweden, and Denmark are based on wholesale sales figures, while those for Northern Ireland are based on general practice prescriptions subsidized under the National Health Service. Reproduced from a publication by King et al. (581), by permission of the senior author.

izers in Norway were about 25% higher than those in Finland and Sweden, but substantially lower than those in Denmark and Iceland.

Wholesale data on drug sales have been collected and monitored in Czechoslovakia since 1955. Between 1965 and 1978, hypnotics were the most commonly sold group of psychoactives; hypnotic sales increased steadily over this period, from 23 to 37 DDD/1000/day. Benzodiazepine anxiolytic sales also increased steadily over this period, reaching 13 DDD/1000/day (270). Sales of benzodiazepine tranquilizers increased further between 1976 and 1981 (1043).

Benzodiazepine tranquilizer use in Czechoslovakia and in the Scandinavian countries from 1966 (or 1970) to 1980, as based on wholesale data and calculated as DDD/1000/day, is shown in fig. 4. The figure also represents comparable data for Northern Ireland, based on retail sales data reported by King et al. (581, described on page 330).

2. Studies of retail data. a. INTERNATIONAL DATA. The sales data discussed below were provided by IMS International, an independent research firm that obtains sales data on pharmaceutical products in a number of countries representing the majority of the world pharmaceutical market. The data are collected through audits of purchases in drug stores; the pharmacies are selected to be nationally representative, and the sampling procedures are similar, insofar as this is practical, across countries. In addition, the data for several countries also include hospital sales, and the data for Switzerland include drugs dispensed directly by physicians.

The figures considered in the following discussion represent calculations based on a standard unit of measurement, developed by IMS International and intended to reflect the quantity of tablets, capsules, or other galenical form of each drug needed on average for a week of treatment (e.g., 20 tablets or capsules); such measurement is subject to obvious disadvantages, but appears to provide a practical basis at least for the type of gross global comparisons considered here. The data presented here represent sales of each drug in any form, i.e., in combination as well as single-ingredient products.

Attention should be focused on the overall patterns indicated rather than on the absolute values associated with individual drugs, countries, or time periods. The accuracy and reliability of these absolute values is uncertain, because of the use of the standard unit of measurement described above and because it is not clear to what extent sampling across countries can be accomplished in a uniform manner. In addition, the set of countries whose sales are taken into account in calculating values reflecting world market totals (tables 12 and 13) has varied across certain years; the effect of this variation is presumably slight, however, since those countries that have been dropped or added appear to represent very small percentages of world sales.

Table 12 presents annual per capita exposure of the adult populations of 15 countries to minor tranquilizers and sedative/hypnotics, based on IMS data. The data presented refer to the latest year for which reliable population statistics are available for each of the countries shown; the populations shown are limited to persons aged 15 or older, since use of these drugs in younger populations is virtually nil. Countries are grouped ac-

TABLE 12

Annual per capita exposure of adult populations (ages 15 and older) to minor tranquilizers and sedative-hypnotics, based on data provided by IMS International (509)

	Yr	Population (millions)*	Tranquilizers		Sedative-hypnotics	
			Millions of standard units†	Per capita exposure per yr	Millions of standard units	Per capita exposure per yr
Countries with data for both hospitals and pharmacies						
Austria	1983	6.1	5.7	0.9	5.9	1.0
Italy	1981	43.9	44.1	1.0	31.4	0.7
Japan	1983	92.6	104.2	1.1	32.5	0.4
Switzerland	1982	5.3	8.2	1.5	7.4	1.4
United Kingdom	1983	45.2	53.3	1.2	46.4	1.0
United States	1984	184.4	218.6	1.2	82.2	0.4
West Germany	1982	51.2	72.2	1.4	60.3	1.2
Countries with data for pharmacies only						
Australia	1983	11.6	14.1	1.2	8.7	0.8
Belgium	1981	7.9	19.0	2.4	7.4	0.9
Brazil	1983	80.7	20.3	0.3	15.2	0.2
France	1983	42.5	129.4	3.0	80.8	1.9
Greece	1981	7.6	8.3	1.1	1.1	0.1
Portugal	1981	7.3	16.1	2.2	2.5	0.3
Spain	1981	28.0	26.6	1.0	9.1	0.3
Venezuela	1984	10.1	2.5	0.2	2.3	0.2

* From Demographic Yearbook; 1984, United Nations, 1986.

† "Standard units" refers to a measure employed by IMS International to denote a quantity of drug sufficient on average for 1 wk of therapy (see text).

cording to whether IMS data reflect sales in both pharmacies and hospitals, or only pharmacy sales. The columns headed "Per capita exposure per yr" indicate the relative exposures of these national populations to minor tranquilizers and to sedative-hypnotics, in terms of annual sales of IMS "standard units" (i.e., a 1-wk supply; see definition above) per capitum.

The table indicates relatively high per capita exposure to minor tranquilizers in France, Belgium, Portugal, and Switzerland, and relatively low exposure in Venezuela, Brazil, and Austria. Per capita exposure to sedatives and hypnotics was relatively high in France, Switzerland, and West Germany, and relatively low in Greece, Venezuela, Brazil, Spain, and Portugal. It is of interest that these data regarding minor tranquilizers tend to agree with population surveys of actual consumption, as described in section V E 1b below, which likewise indicate relatively high levels of use in France, Belgium, and Switzerland.

Table 13 presents trends in shares of the minor tranquilizer market for the 11 world leaders from 1981 through 1985. The figures are calculated from IMS International data for 1985, which reflect sales for 23 countries. In addition to the caveats mentioned above, it should be noted that, in 1985, the data for some countries reflected both pharmacy and hospital sales; in previous years, only pharmacy data were represented. Nevertheless, the trends shown seem quite consistent, suggesting that they are valid representations at least of gross global changes.

As table 13 indicates, then, 9 of the 11 leading minor tranquilizers in 1985 were benzodiazepines, which together accounted for 76% of all minor tranquilizer sales; these percentages of the world market for the leading tranquilizers have not changed substantially between 1981 and 1985. Over this period, the share commanded by diazepam has decreased and that commanded by lorazepam has increased, so that each of these compounds now has 20% of the world market. Both bromazepam and alprazolam sales have increased in percentage of the total market, while the percentages represented by oxazepam and chlordiazepoxide have declined slightly. It might be noted that these changes generally correspond to the length of time the various compounds have been available; older compounds have tended to lose market share, while newer compounds have tended to gain.

TABLE 13

Percentage share of world market for leading minor tranquilizers, based on data provided by IMS International (509)

	1981	1982	1983	1984	1985
1. Lorazepam	16	18	19	19	20
2. Diazepam	28	26	23	21	20
3. Oxazepam	11	11	10	10	9
4. Bromazepam	5	6	7	7	8
5. Clorazepate	7	7	7	7	6
6. Hydroxyzine	5	5	5	6	6
7. Chlordiazepoxide	7	6	6	5	5
8. Meprobamate	5	5	5	5	5
9. Alprazolam			1	3	4
10. Prazepam	2	2	2	2	2
11. Clotiazolam	1	2	2	2	2

TABLE 14

Percentage share of world market for leading sedatives-hypnotics, based on data provided by IMS International (509)

	1981	1982	1983	1984	1985
1. Phenobarbital	18	18	18	18	17
2. Triazolam	2	3	6	9	11
3. Nitrazepam	12	12	11	10	9
4. Flurazepam	9	9	8	7	6
5. Flunitrazepam	4	5	5	5	6
6. Temazepam	1	2	3	4	5
7. Ergotamine	6	5	5	4	4
8. Acepromet azine	3	3	3	3	3
9. Amobarbital	2	<2	<2	<2	<2

Table 14 presents similar data for the leading sedative-hypnotic drugs, subject to the same limitations and caveats discussed above with respect to the tranquilizer data. These data apparently include agents used for daytime sedation as well as for promotion or maintenance of sleep. The nine leading sedative-hypnotics in 1985 together accounted for 61% of the total market; this indicates that there is greater diversity in sedative-hypnotic prescriptions than there is for tranquilizer prescriptions, since the leading tranquilizers shown in table 13 accounted for 87% of the total tranquilizer market. Of these leading sedative-hypnotics, the five benzodiazepines collectively accounted for 37% of world sales in 1985, up from 28% in 1981. Although the table shows only the leading agents, it seems clear that benzodiazepines represent a minor proportion of all sedative-hypnotic sales, in contrast to their dominance of the tranquilizer market. Indeed, in 1985 phenobarbital led the market by a considerable margin over triazolam, the leading benzodiazepine sedative-hypnotic. The table also indicates that there has been more change over the period shown among the benzodiazepines than among other compounds. Triazolam, temazepam, and flunitrazepam have increased in market shares, while nitrazepam and flurazepam shares have declined.

It is of interest to consider the variation in these markets by individual country. This information is available in the IMS data for 1984. The data shown in tables 15 and 16 represent relative shares of the minor tranquilizer market and of the sedative-hypnotic market, respectively, in each of 19 countries, including 10 European nations; 5 Central and South American nations; as well as Australia, Japan, South Africa, and the United States. Numbers in parentheses to the right of each country name are the percentages of the total world tranquilizer or sedative-hypnotic market represented by all sales (not only those of the leading drugs shown) in that country.

As indicated in table 15, in 1984 the U.S. and France together accounted for 43% of the total market for minor

TABLE 15

Sales of minor tranquilizers by market share (%) in 1984, based on data provided by IMS International

Europe

Austria (0.7)*		Belgium (2.7)		France (18.7)		Germany (7.5)	
Bromazepam	28	Lorazepam	34	Lorazepam	36	Oxazepam	39
Lorazepam	24	Bromazepam	23	Clorazepate	14	Bromazepam	21
Diazepam	9	Oxazepam	10	Oxazepam	9	Diazepam	14
Oxazepam	9	Diazepam	7	Clobazam	8	Lorazepam	8
Prazepam	6	Clorazepate	5	Bromazepam	6	Clorazepate	6
Clorazepate	4	Meprobamate	3	Diazepam	6	Clobazam	3
Clobazam	2	Alprazolam	3	Meprobamate	5	Prazepam	3
Haloperidol	2	Clobazam	3	Prazepam	4	Chlordiazepoxide	2
Meprobamate	2						
Great Britain (6.5)		**Greece (1.4)**		**Italy (6.3)**		**Portugal (2.4)**	
Diazepam	39	Lorazepam	30	Lorazepam	46	Nitrazepam	28
Lorazepam	23	Bromazepam	15	Diazepam	16	Bromazepam	23
Chlordiazepoxide	9	Stedon	11	Bromazepam	15	Oxazepam	10
Temazepam	8	Pimethixene	9	Prazepam	4	Diazepam	7
Clorazepate	5	Diazepam	7	Oxazepam	3	Clorazepate	5
Oxazepam	5	Clorazepate	7	Clorazepate	2	Meprobamate	3
Clobazam	3	Clobazam	4	Desmethyldiazepam	2	Alprazolam	3
Alprazolam	2	Prazepam	3	Clobazam	1	Clobazam	3
Spain (4.1)		**Switzerland (1.0)**					
Diazepam	18	Bromazepam	30				
Lorazepam	16	Oxazepam	28				
Clorazepate	14	Lorazepam	15				
Pyridoxine	13	Diazepam	9				
Bromazepam	8	Chlorazepate	3				
Clobazam	3	Alprazolam	1				
Chlordiazepoxide	3	Chlordiazepoxide	1				
Meprobamate	2	Prazepam	1				
		Medazepam	1				
		Camazepam	1				

Latin America

Argentina (4.4)		Brazil (2.8)		Columbia (0.4)		Mexico (1.4)	
Bromazepam	27	Lorazepam	19	Lorazepam	27	Lorazepam	30
Lorazepam	23	Diazepam	16	Bromazepam	23	Diazepam	18
Diazepam	9	Bromazepam	15	Diazepam	15	Bromazepam	13
Clorazepate	3	Clobazam	7	Oxazepam	4	Clorazepate	9
Clobazam	2	Haloperidol	5	Clobazam	4	Clobazam	6
Cloxazolam	2	Alprazolam	4	Prazepam	4	Oxazepam	4
Prazepam	1	Clorazepate	1	Medazepam	4	Hydroxyzine	3
		Chlordiazepoxide	1			Chlordiazepoxide	2
Venezuela (0.3)							
Lorazepam	26						
Clorazepate	26						
Diazepam	16						
Bromazepam	16						

Other countries

Australia (2.1)		Japan (7.8)		South Africa (0.7)		United States (23.7)	
Oxazepam	49	Oxazepam	26	Lorazepam	38	Diazepam	35
Diazepam	25	Chlordiazepoxide	16	Oxazepam	21	Lorazepam	12
Temazepam	4	Medazepam	9	Bromazepam	15	Clorazepate	11
Lorazepam	2	Clotiazepam	9	Diazepam	11	Alprazolam	10
Bromazepam	2	Hydroxyzine	8	Clobazam	6	Chlordiazepoxide	9
Chlordiazepoxide	2	Diazepam	6	Prazepam	4	Hydroxyzine	7
Clorazepate	1	Bromazepam	1	Clorazepate	2	Meprobamate	6
				Chlordiazepoxide	2	Oxazepam	3

* Percentage of world tranquilizer market represented by *all* sales in this country.

tranquilizers; the next most substantial proportions of the market were represented by Japan, Germany, Great Britain, and Italy. As previously indicated in table 13, table 15 shows that the benzodiazepines predominated among minor tranquilizers sold in all countries studied. No single benzodiazepine clearly predominated across countries. The most popular agents in the European countries were lorazepam, bromazepam, diazepam, and

oxazepam; those most popular in the Central and South American countries were the same ones, with the exception of oxazepam. Oxazepam, however, accounted for 49% of all tranquilizer sales in Australia and also held the largest market share in Japan.

Table 16 presents similar numbers for shares of the sedative-hypnotic markets in these same 19 countries. As was the case also for tranquilizers, France and the U.S. together accounted for over 40% of the total market for sedative-hypnotic drugs; the next most substantial

TABLE 16

Sales of sedative-hypnotics by market share (%) in 1984, based on data provided by IMS International (509)

Europe

Austria (1.3)*		Belgium (2.0)		France (21.8)		Germany (13.9)	
Flunitrazepam	13	Flunitrazepam	19	Triazolam	15	Phenobarbital	5
Ergotamine	13	Nitrazepam	13	Phenobarbital	14	Ergotamine	5
Nitrazepam	6	Phenobarbital	13	Clorazepate	9	Flunitrazepam	9
Promazine	6	Ergotamine	12	Flunitrazepam	8	Triazolam	9
Clomethiazole	2	Triazolam	12	Nitrazepam	8	Nitrazepam	6
		Lormetazepam	3	Aceprometazine	7	Lormetazepam	4
		Clomethiazole	1	Clomethiazole	3	Ergotamine	4
		Amobarbital	1	Mepyramime maleate	2		
				Phenobarbital	2		

Great Britain (10.3)		Greece (0.3)		Italy (7.3)		Netherlands (2.4)	
Nitrazepam	39	Flunitrazepam	42	Phenobarbital	17	Nitrazepam	24
Temazepam	15	Triazolam	17	Flurazepam	9	Phenobarbital	13
Flurazepam	11	Phenobarbital	17	Flunitrazepam	9	Flurazepam	9
Phenobarbital	10	Nitrazepam	8	Flurazepam	3	Temazepam	9
Triazolam	6	Passiflorine	8	Nitrazepam	2	Flunitrazepam	8
Amobarbital	3			Lormetazepam	4	Lormetazepam	1
Lormetazepam	2			Ergotamine	4	Ergotamine	1
Flunitrazepam	1					Valtrate	1
						Butabarbital	1

Portugal (0.8)		Spain (2.7)		Switzerland (1.7)	
Phenobarbital	31	Phenobarbital	20	Flunitrazepam	16
Ergotamine	19	Flunitrazepam	17	Phenobarbital	13
Triazolam	16	Triazolam	14	Ergotamine	10
Flunitrazepam	9	Flurazepam	9	Nitrazepam	9
Flurazepam	6	Nitrazepam	5	Triazolam	6
Nitrazepam	3	Lormetazepam	2	Flurazepam	6
Lormetazepam	3			Lormetazepam	1

Latin America

Argentina (1.7)		Brazil (4.0)		Columbia (0.2)		Mexico (0.8)	
Flunitrazepam	27	Phenobarbital	50	Nitrazepam	17	Passiflorine	17
Phenobarbital	25	Flurazepam	6	Flurazepam	17	Triazolam	13
Nitrazepam	7	Triazolam	5	Flunitrazepam	17	Calcium bromolactobi	13
Triazolam	4	Flunitrazepam	5	Passiflorine	17	Nitrazepam	10
Ergotamine	3	Passiflorine	4			Flunitrazepam	10
Clomethiazole	1	Nitrazepam	3			Phenobarbital	10
		Ergotamine	1			Ergotamine	10
						Flurazepam	3
						Alepsal	3

Venezuela (0.5)	
Phenobarbital	27
Calcium bromalactobi	17
Nitrazepam	5
Ergotamine	5

Other countries

Australia (2.3)		Japan (4.0)		South Africa (0.6)		United States (18.6)	
Nitrazepam	41	Phenobarbital	25	Phenobarbital	22	Phenobarbital	34
Temazepam	14	Ergotamine	25	Triazolam	13	Flurazepam	17
Chloral hydrate	8	Nitrazepam	14	Nitrazepam	9	Temazepam	9
Amobarbital	7	Triazolam	13	Flunitrazepam	9	Triazolam	8
Flunitrazepam	5			Ergotamine	9	Secbutabarbital	5
Methyl phenobarbital	5			Flurazepam	4	Ergotamine	4
Flurazepam	1			Valtrate	4	Mepyramine maleate	2
Pentobarbital	1			Temazepam	4	Secobarbital	2
Butabarbital	1						

* Percentage of world sedative-hypnotic market represented by *all* sales in this country.

proportions of this market were represented by Germany, Great Britain, and Italy.

Benzodiazepines do not predominate among sedative-hypnotic markets to the extent that they do among tranquilizer markets. Among the leading sedative-hypnotics, benzodiazepines predominate in 8 of the 10 European countries studied; in 2 of the 5 Central and South American countries; and in Australia and South Africa, but not Japan or the U.S. Indeed, among both the European and the Central and South American countries, as well as in the U.S., Japan, and South Africa, the leading sedative-hypnotic agent was phenobarbital; the next most popular agents in the European countries were nitrazepam, flunitrazepam, and triazolam, and the next most popular agents in the Central and South American countries were flunitrazepam and nitrazepam.

b. NATIONAL DATA. **i. United States.** Data on retail drug sales in the U.S. are collected in the National Prescription Audit (NPA; 505) from a representative sample of chain and independent pharmacies. NPA data indicate that sales of minor tranquilizer prescriptions reached a peak in 1975 of 103 million (including 88 million benzodiazepine prescriptions), declined to 67 million in 1981, and then increased slightly again, reaching 71 million in 1984 (899, 57). While the total number of prescriptions for hypnotics (chiefly barbiturates) decreased by 41% between 1971 and 1976, prescriptions for benzodiazepine hypnotics increased 4-fold in this period (899). Sales of all hypnotics meanwhile continued to decrease until 1980, and then showed a slight increase (55); benzodiazepine hypnotic sales have continued to increase through 1985.

Table 17 shows the total numbers of prescriptions for benzodiazepine minor tranquilizers and hypnotics dispensed in 1983, 1984, and 1985 (in parentheses at the head of each column; the numbers given represent millions of prescriptions). The data indicate that benzodiazepine tranquilizer sales increased slightly in this period, and that benzodiazepine hypnotic sales increased somewhat more steeply. The table also presents the relative shares of these markets commanded by each of the individual agents available in the U.S. These relative shares and the trends of change seen in the table are similar to those reflected in the international data discussed previously.

TABLE 17

Shares of total prescriptions for benzodiazepine minor tranquilizers and hypnotics dispensed in U.S. retail pharmacies (%), based on data from the National Prescription Audit (505)

	1983	1984	1985
Minor tranquilizers	(58.0)*	(59.5)	(61.0)
Diazepam	45	41	37
Alprazolam	8	13	19
Lorazepam	15	15	16
Chlorazepate	13	12	12
Chlordiazepoxide	11	10	9
Oxazepam	5	4	4
Prazepam	3	3	3
Halazepam	<1	<1	<1
Hypnotics	(16.8)	(18.6)	(20.0)
Flurazepam	61	48	38
Triazolam	12	25	34
Temazepam	27	27	27

* Numbers in parentheses, total millions.

ii. Canada. An analysis of IMS data on drug sales in Canada (147) found that benzodiazepines sales were stable from 1978 to 1982 (at 33 DDD/1000/day) and increased in 1983 and 1984 (reaching 41 DDD/1000/day). The increase in total benzodiazepine use between 1978 and 1984 was attributed to a sharp increase in sales of short-acting agents, while sales of long-acting benzodiazepines declined; and to an increase in sales of benzodiazepine hypnotics, while sales of benzodiazepine anxiolytics remained stable during this period.

iii. Great Britain. The Department of Health and Social Security (DHSS) provides data on sales of prescription drugs in retail pharmacies in Great Britain. The findings described below were based on analyses of these data. Parish (848) found that, between 1965 and 1970, sales of barbiturate hypnotics decreased by 24%, while sales of nonbarbiturate hypnotics (chiefly of Mandrax, a combination of methaqualone and diphenhydramine; and of nitrazepam, both of which were introduced in the United Kingdom in 1965) increased by 145%. Among ataractics, while sales of meprobamate and of barbiturates used as ataractics declined, overall sales of minor tranquilizers increased by 220%, due to increases in prescriptions chiefly of chlordiazepoxide and diazepam.

Williams (1147) found that, between 1965 and 1975, prescriptions for barbiturate hypnotics decreased by 57%, and prescriptions for nonbarbiturate hypnotics (principally benzodiazepines) increased by 291%. Between 1966 and 1977, prescriptions for tranquilizers (presumably including major as well as minor tranquilizers) increased by 78%. Comparison of the trends for 1970 to 1975 with those for 1965 to 1970 indicated that the rate of decrease in sales of barbiturate hypnotics had slowed down, as had the rates of increase in sales of nonbarbiturate hypnotics and of tranquilizers (1148).

iv. Northern Ireland. The findings described below are based on analyses of data on psychotropic drug prescriptions subsidized by the National Health Service, which have been computerized since 1966. The data are computed in terms of the DDD unit of measurement, permitting comparisons with other countries using this system (see section V A, page 321).

Beginning with the introduction of nonbarbiturate hypnotics in 1966 (i.e., nitrazepam and a methaqualone-diphenhydramine combination), hypnotic prescriptions increased from 30 to 44 DDD/1000/day in 1973, and appeared to have leveled off by 1974, when nitrazepam had become the most frequently prescribed hypnotic. These data were compared with similar data for Norway,

where a similar increase occurred in the same period, reaching 42 DDD/1000/day; and for Great Britain, where hypnotic prescription sales (especially barbiturates) were higher in 1966, but had declined by 1973 to a level similar to that in Northern Ireland (274).

King et al. (581) examined the Central Services Agency data on prescriptions of various classes of psychotropics between 1966 and 1980. They found that prescriptions for benzodiazepines (both tranquilizers and hypnotics) increased from 1966 to a peak in 1976, and after a 3-yr plateau began to decline in 1979. The annual rate of increase for all tranquilizers was about 20% from 1966 to 1969, then about 10% from 1970 to 1976. Over this entire decade, the DDD/1000/day for tranquilizers increased from 10.7 in 1966 to 34.1 in 1976. Hypnotic prescriptions continued to increase until 1979, after which they declined slightly to 1980. The investigators undertook a related study of 24 group practices in the Belfast area in 1979 and applied multiple regression analysis in an attempt to explain the wide variations observed in patterns of tranquilizer and hypnotic prescribing. The results indicated that 92% of the variance in hypnotic prescriptions could be accounted for by the relative proportions of recipients who were elderly (over 65) and of those who were females between 45 and 59 yr of age; but none of the factors studied was found to explain a significant proportion of the variance in tranquilizer prescriptions.

These investigators (581) also compared the data from Northern Ireland with data for other countries. The per capita rate of benzodiazepine prescribing in Northern Ireland was about 20 to 30% higher than that in Great Britain between 1966 and 1978, while the rate of hypnotic prescribing was slightly lower than that in Great Britain. Northern Ireland sales of benzodiazepine tranquilizers were compared with those in several other European countries using the DDD/1000/day unit of measurement, including Iceland, Denmark, Norway, Sweden, Finland, and Czechoslovakia (see fig. 4). From 1966 to 1976, benzodiazepine tranquilizer exposure increased in Northern Ireland more rapidly than in these other countries, surpassing the Norwegian rate in 1972 and then remaining third after Iceland and Denmark.

v. Republic of Ireland. Analysis of data regarding the number of benzodiazepines and barbiturates dispensed under subsidies by the General Medical Service (GMS) of the Republic of Ireland indicated that sales of diazepam, nitrazepam, chlordiazepoxide, flurazepam, medazepam, and lorazepam (ranked in order of volume) proved equivalent to 50.1 DDD/1000/day in 1973, 62.0 DDD/1000/day in 1975, and 64.5 DDD/1000/day in 1977; the increase over this period was due chiefly to increases in sales of nitrazepam and diazepam. These sales rates appear to have been somewhat higher than those for the population not covered under GMS subsidies, possibly because the GMS population included a larger proportion of elderly patients. These data on sales of five benzodiazepines (diazepam, nitrazepam, chlordiazepoxide, flurazepam, and medazepam) were compared with comparable data for Northern Ireland, Iceland, and Finland. In 1977, consumption of these drugs in the Republic of Ireland was equivalent to 39 DDD/1000/day; in Northern Ireland it was 52 DDD/1000/day; in Iceland it was 72 DDD/1000/day; and in Finland (at least in 1975) it was 25 DDD/1000/day (202).

vi. Iceland. Retail sales of benzodiazepine tranquilizers and hypnotics increased from an equivalent of 65.5 DDD/1000/day in 1970 to 91.2 DDD/1000/day in 1976; following the imposition of various Government measures to restrict use of these and certain other medications, benzodiazepine sales then declined to the equivalent of 71.8 DDD/1000/day in 1978 (825).

vii. Australia. Mant and Hall (710) examined sales of various types of psychoactive drugs; they used data on prescriptions subsidized under the Government's Pharmaceutical Benefits Scheme (PBS), as well as data on retail sales provided by IMS Australasia, Ltd. Sales of minor tranquilizers in general, and of diazepam in particular, markedly increased in the early 1970s and began a clear downturn by 1976 to 1977; these trends, which the investigators noted corresponded to similar trends in other countries, were not apparently affected by changes in drug prices nor by changes in Government subsidies that occurred during this period. Both the Government and IMS data indicated that sales of "hypnosedatives," including both barbiturates and nonbarbiturates used for daytime sedation as well as for treatment of sleep disturbances, declined substantially between 1967–1968 and 1976–1977; during this period, sales of barbiturates showed a steady linear decline, while sales of nitrazepam markedly increased, at least until 1975–1976.

Carmody et al. (156) examined two sets of data collected by the Australian government, covering benzodiazepine prescriptions reimbursed under the "general pharmaceutical benefits scheme" and under the "pensioner medical benefits scheme" between 1972 and 1975. Their analysis indicated that 35% of benzodiazepine prescriptions during this period were reimbursed under the pensioners' scheme, although pensioners accounted for less than 10% of the population; thus the per capita rate of benzodiazepine consumption was estimated to be 4 times greater for the elderly than for the remainder of the population covered under Government subsidies. In contrast to the findings of Mant and Hall, described above (710), these investigators found that reimbursed benzodiazepine prescriptions remained at a constant level between 1972 and 1975, except for an increase in 1973 when Government prescribing criteria were altered.

With respect to the disproportionate per capita representation of the elderly population among recipients of benzodiazepine prescriptions, as noted by Carmody et al. (156; see above), it is of interest that this disparity was apparently not limited to the use of benzodiazepines. Hall (424) has reported that, during the period of 1972

to 1981, there were about 4 drug prescriptions per annum per capita of the general population (excluding pensioners), but about 20 prescriptions per annum per capita for the pensioner population; thus the age difference with respect to benzodiazepine prescriptions, as reported by Carmody et al., was less than the age difference with respect to all prescriptions. Hall (424) also found that, while some shifts in prescription rates had occurred among the benzodiazepines in conjunction with changes in Government subsidies between 1977–1978 and 1980–1981, the total use of benzodiazepines over this period had not changed substantially. The rate in 1980–1981 was 156 DDD/1000/day. This figure cannot be compared directly with the data presented in the Australian reports described above, which were not computed according to the DDD unit of measurement; but it does seem dramatically higher than DDD rates that have been reported for other countries, including the Scandinavian countries, Northern Ireland, and Czechoslovakia (discussed previously in this section).

c. REGIONAL AND HOSPITAL DATA. There have been a number of studies of the use of benzodiazepines based on records of prescriptions dispensed in limited geographical regions and in hospitals. Table 18 presents certain studies of this kind, in which sales of minor tranquilizers and/or sedative-hypnotics were given or could be calculated as percentages of total prescriptions dispensed, of the total population of potential consumers, or both. These percentages tend to be fairly consistent among studies (except for the report by Federspiel et al., 285) and are in good agreement with the rates of use of these medications found in physician and prescription surveys (discussed in section V D) as well as in community surveys of consumption (section V E).

Two other groups of regional and hospital studies of this kind are also of interest, namely, drug utilization review studies that have attempted to identify and measure various kinds of abuse based on pharmacy data, and a series of Swedish studies in which people who filled psychotropic prescriptions were followed for several years to examine patterns of use and potential abuse.

i. Drug utilization review studies. Maronde et al. (715) described a computer-based system that permitted monitoring of the more than 600,000 prescriptions dispensed annually to outpatients at the Los Angeles County-University of Southern California Medical Center. Twelve drugs of potential abuse were selected for a special utilization review; these included propoxyphene, methylphenidate, and several barbiturates, as well as both benzodiazepine and nonbenzodiazepine minor tranquilizers. Physicians at the Medical Center established arbitrary dosage limits beyond which single or multiple prescriptions for each of these drugs would be classified as excessive. The limits for chlordiazepoxide (5, 10, or 25 mg) and for diazepam (2, 5, or 10 mg) were 100 capsules or tablets per single prescription, or 150 capsules or tablets that might be in a patient's possession at a single time through multiple prescriptions from the same physician or different physicians. Examination of the records of prescriptions dispensed during 3 mo of 1971 showed that diazepam, chlordiazepoxide, propoxyphene, and phenobarbital were the drugs most frequently prescribed in amounts considered excessive, and these same drugs were also the most frequently involved in excessively frequent multiple prescriptions for the same patient; the investigators pointed out that such frequent multiple prescribing in some cases was the result of "doctor shopping," i.e., patients visiting more than one physician expressly to obtain large amounts of a given drug.

A later study by Maronde and Silverman (716), which used the same database as that described in the earlier report (715), consisted in a review of the utilization of chlordiazepoxide, diazepam, meprobamate, secobarbital, and pentobarbital over a 12-mo period (dates not specified). Prescriptions for chlordiazepoxide (5, 10, or 25 mg) or diazepam (2, 5, 10 mg) for an individual patient were considered excessive if they provided more than 600 units (tablets or capsules) in the course of the year. According to these criteria, of all patients receiving prescriptions for the 5-mg strength of chlordiazepoxide, 1.2% received excessive amounts; as did 4.1% of those receiving the 10-mg strength, and 2.4% of those receiving the 25-mg strength. These excessive prescriptions accounted for 44.2% of all the chlordiazepoxide dispensed during the year. Excessive amounts of diazepam were dispensed to 1.6% of all patients receiving the 2-mg strength of this drug, to 2.2% of those receiving the 5-mg strength, and to 1.6% of those receiving the 10-mg strength. Prescriptions for these patients accounted for 40.8% of all the diazepam dispensed during the year. For the sake of comparison, it is of interest to note that, again according to the study criteria, excessive amounts of meprobamate were given to 6.2% of all patients receiving the 400-mg strength; excessive amounts of secobarbital were given to 3.6% of all patients receiving the 100-mg strength; and excessive amounts of pentobarbital were given to 1.3% of those receiving the 100-mg strength of this drug. The investigators further noted that some patients received amounts of the drugs studied far in excess of the study criteria.

Scrivens et al. (991) conducted a retrospective review of prescriptions for diazepam and for methyldopa dispensed over a 6-mo period at the Tampa (FL) Veterans Administration Medical Center; the dates of the survey period were not specified. They found that, of 91 patients who had received diazepam prescriptions, 58.2% had refilled their prescriptions early (19.8%), had filled duplicate prescriptions from the same or another physician (3.2%), or both (35.2%). Of 75 patients receiving methyldopa prescriptions, 54.7% had refilled their prescriptions early (20.0%), had filled duplicate prescriptions (14.7%), or both (20.0%).

In sum, these studies of drug utilization are interesting

TABLE 18
Regional and hospital prescription sales

Study	Source of data	Area represented	Date(s) of survey	Drugs	% of total Rx*	% of total population
Stolley et al., 1972 (1052)	Computerized prescription recording system monitoring 85% of Rx dispensed (excluding hospitals) for a community of 112,000 people	U.S.A.: mid-Atlantic	1968	Tranquilizers (chiefly chlordiazepoxide and diazepam)	7.7	5.4
				Hypnotics/sedatives	3.6	2.9
Mayfield and Morrison, 1973 (732)	All Rx dispensed by Veterans Administration hospital pharmacy to outpatients: 31,867 Rx for yr of study	U.S.A.: Durham, NC	1970	Minor tranquilizers (chlordiazepoxide, diazepam, meprobamate)	5.2	
Rosenberg et al., 1974 (935)	Sample of Rx invoices submitted to New York City Medicaid Program on a single day. Program enrollment was 1.4 million people.	U.S.A.: New York, NY	May 1971	Tranquilizers and antidepressant-tranquilizer combinations	7.1	
				Sedatives and hypnotics	3.3	
Federspiel et al., 1976 (285)	All outpatient pharmacy claims under TN Medicaid Program: total claims over 200,000 in mo of study	U.S.A.: TN	July 1974	Tranquilizers (presumably both major and minor)	12.9	
				Diazepam	5.8	
				Barbiturates	34.3	
Cooperstock and Sims, 1971 (200)	Sample of Rx dispensed by retail pharmacies and hospital outpatient pharmacies: estimated 57 million Rx dispensed per yr	Canada: Toronto, Ontario	1 wk in Oct. 1965 and 1 wk in Apr. 1966	Minor tranquilizers	4.3	
				Meprobramate and skeletal muscle relaxants	1.2	
				Sedatives and hypnotics	10.6	
Power et al., 1983 (882)	All psychotropic Rx dispensed under the Saskatchewan Prescription Drug Plan. Total Rx per study yr averaged 3,914,250. Total population averaged 930,000.	Canada: Saskatchewan	1977–1980	Minor tranquilizers		8.7
				Sedatives/hypnotics		2.7
				Phenobarbital		0.9
Knight, 1970 (587)	All prescriptions dispensed by hospital outpatient pharmacy: over 13,000 Rx in period of study.	United Kingdom: London (?)	Jan.-Mar., 1968	Minor tranquilizers (including barbiturates)	15.0	
				Benzodiazepine tranquilizers	11.0	
				(Diazepam)	8.0	
				Hypnotics	4.0	
				(Nitrazepam)	1.0	
Boethius, 1977 (97)	Sample of outpatient Rx dispensed in county of Jämtland, Sweden. Total sample was about 16,000 persons representing 14% of total population.	Sweden: Jamtland County	1974	Psychotropics	15.9	18.0

* Rx, prescription(s).

but difficult to interpret. The studies by Maronde and coworkers indicate that a small number of patients (and physicians) may be responsible for a large proportion of excessive prescribing of benzodiazepines and of certain other drugs—and indeed for a large proportion of all of these drugs that are dispensed, at least under the conditions studied. However, as Maronde and Silverman (716) pointed out, the data examined provided no information

as to whether patients actually consumed these drugs, stored them in their medicine cabinets, or sold or gave them to other individuals. In the conditions studied by Maronde and coworkers and by Scrivens and coworkers, the cost of virtually all prescriptions was subsidized or reimbursed by third-party payment programs. In this connection, Solomon et al. (1028) found that the rate of overutilization of various medications was 79.7% among third-party-payment patients versus 47.5% among patients who had to pay for their prescriptions themselves. Like Scrivens et al. (991), Solomon and coworkers also found that there was no significant difference in rates of overutilization of psychotropics and of antihypertensives; when drugs are available at little or no cost to the patient, patients may tend to "stockpile" them for possible future use. In any case, it appears that these prescription-seeking and -filling behaviors are not necessarily specific to any particular drug classes. Thus, these behaviors cannot be taken as a direct measure of abuse, though they do compel attention to problems of overprescribing, which may be inherent particularly in large clinical complexes.

ii. Studies of individuals' psychotropic drug purchases over time. Boethius and Westerholm have reported a series of studies of purchases of psychotropic drugs by individuals over several-year periods in the county of Jämtland, Sweden, where a system of continuous registration of outpatient prescription dispensing was started in 1968. Jämtland is a predominantly rural county, which at the time of these studies had a population of about 130,000 people. An initial study (99) followed patients who filled prescriptions for hypnotics, sedatives, or minor tranquilizers (most frequently benzodiazepines) between March 1968 and June 1969. The 493 patients were considered in two groups, those who filled only one such prescription during this period, and those who filled at least eight. By 1973, both groups had significantly decreased their purchases of these drugs. Over the 5 yr studied, only one patient in each group had significantly decreased the intervals between refills for medications.

A later study (100) was able to take advantage of a more representative sample of the population of the country. This study found that 2,566 patients, representing 15.5% of the total population, filled prescriptions for hypnotics, sedatives, or minor tranquilizers in 1970. These patients were divided into three groups, based on the numbers of such prescriptions filled in 1970 (7.4%, one prescription; 6.9%, two to six; 1.2%, seven or more). Within each group there was a highly significant intraindividual reduction in 1975 purchases as compared with those in 1970. However, 10 to 23% of the patients in each group had increased their purchases of these drugs between 1970 and 1975; of the 30 individuals (1.2%) who markedly increased their purchases, examination of the purchase records year by year suggested that 15 (0.6%) had developed a regular purchase pattern. Benzodiazepines accounted for about 45% of the prescriptions in 1970 and about 60% in 1975. Among those 15 patients who developed regular use patterns, benzodiazepines accounted for most prescriptions, in four cases together with other drugs. Four patients (0.2%) showed indications of overuse or abuse, including increasingly frequent purchases and simultaneous use of prescriptions from different physicians.

In a final brief report, Boethius (98) described a later study of a cohort of 234 residents of Jämtland County who filled their first prescription for a hypnotic or sedative (a benzodiazepine in three of four instances) in 1976. Three-fourths of these patients did not purchase any other sedative-hypnotic drugs over the following 5 yr. However, 21% were still purchasing such medications in 1981. Of 66 patients originally prescribed nitrazepam, 16% developed a pattern of regular use between 1976 and 1981, as did 9% of patients receiving other benzodiazepines, and 6% of patients receiving nonbenzodiazepine sedative-hypnotics.

3. Summary and discussion. Although sales data provide only gross and quite indirect information about consumption of benzodiazepines, they represent the most direct indicator of their supply, distribution, and availability in various countries. In addition, examination of these data over time provides a useful perspective on trends of change in these patterns. However, sales of drugs are determined by a number of factors unrelated to their pharmacology or abuse liability. Thus, indications that a particular drug is gaining in market share do not necessarily warrant concern about the possibility that it is being prescribed inappropriately nor that it is in great demand for purposes of misuse.

Individual benzodiazepines are not marketed in a uniform fashion throughout the world. They are not sold at all in some countries; there are wide variations in their availability among the countries where they are sold. For example, a relatively limited number of benzodiazepine products is on the market in the U.S.; whereas many more compounds are available in Japan, some of which are not widely available elsewhere (714). Furthermore, the world pattern of availability of individual benzodiazepines has changed rapidly, and new entries in the marketplace promise further change. Finally, it should be noted that it is difficult to find reliable data on availability of benzodiazepines (and of other drugs) for most of the countries of the world.

a. STUDIES OF WHOLESALE DATA. Wholesale data for the U.S indicate that, in 1985, psychotherapeutic agents accounted for 7.5% of all drugstore and hospital purchases of ethical drugs, of which 48% were benzodiazepine anxiolytics.

Wholesale drug sales in the Scandinavian countries and Czechoslovakia have been reported in terms of DDD/1000/day (see section V A, page 321). In terms of this measure, sales of benzodiazepines increased in all of the Scandinavian countries except Sweden, and in Czechoslovakia, from the mid-1960s through at least 1980, largely displacing sales of barbiturates. Sales of

benzodiazepine minor tranquilizers decreased in Sweden after 1969, and sales of benzodiazepine hypnotics decreased in Finland and Sweden between 1966 and 1977. Sales of benzodiazepine minor tranquilizers throughout this period were roughly similar for Finland, Norway, and Sweden, with higher numbers reported for Denmark and Iceland. In Czechoslovakia, sales of benzodiazepine anxiolytics throughout this period were considerably lower than in the Scandinavian countries, but use of benzodiazepine hypnotics was similar to that in Norway and Sweden.

b. STUDIES OF RETAIL DATA. International marketing data representing retail sales indicated that nine of the leading minor tranquilizers in 1985 were benzodiazepines, which together accounted for 76% of the world market; this picture has been relatively stable over the last 5 yr. In this period, diazepam and lorazepam together have accounted for about 40% of the world market; in 1981 diazepam had the greater share, but in 1985 these two compounds each had about 20% of the market.

There is greater diversity in prescribing of sedatives and hypnotics, of which the five leading benzodiazepines in 1985 accounted for only 37% of the world market (up form 28% in 1981). Phenobarbital remains the most frequently sold sedative-hypnotic; triazolam is the leading benzodiazepine hypnotic.

The U.S. and France together account for over 40% of world sales of both minor tranquilizers and sedative-hypnotics.

National studies of retail prescription sales for the U.S., the United Kingdom, Northern Ireland, the Republic of Ireland, Iceland, and Australia uniformly showed increases in sales of benzodiazepines (anxiolytics in all countries, hypnotics in some) from the mid- or late 1960s to at least the early 1970s. This increase slowed in the early 1970s in the U.S. and the United Kingdom; sales in the U.S. decreased from 1973 to 1979, and then began a second gradual increase. Similarly, sales in Iceland and Australia began a decrease after about 1976; sales in Northern Ireland leveled off in the mid-1970s and began a decrease in 1979.

c. REGIONAL AND HOSPITAL DATA. A number of studies of the use of benzodiazepines based on records of prescriptions dispensed in limited geographical regions and in hospitals have provided data permitting the calculation of the percentage these sales represent of all prescriptions, or the percentage of the total population who received such prescriptions. These figures tend to be fairly consistent among studies, and are in good agreement with rates of use of these medications as reported from physician and community surveys.

A few computer-based drug utilization studies have been reported from large clinical complexes. These studies have focused on evidences of inappropriate prescribing. They indicate that, under certain conditions, including third-party payment for patient access to a variety of health care facilities and providers, a small number of patients may be responsible for a large proportion of prescribed benzodiazepines and certain other drugs. However, since these studies have not attempted to measure actual consumption, their bearing on abuse liability must be interpreted with caution.

A series of studies in a rural county of Sweden, where outpatient prescription dispensing is continuously recorded, has followed individuals' purchases of psychotropic drugs over 5-yr periods. These studies have found that patients tend to decrease such purchases over time, regardless whether their purchases were frequent or infrequent at the beginning of the study period. A minority of patients was found to increase such purchases over a 5-yr period, and a very small percentage showed evidence of possible abuse.

D. Surveys of Prescribing Patterns

Surveys of physicians and of prescription records provide a global perspective on the ways in which benzodiazepines are prescribed—by what medical specialties, in what clinical settings, for what demographic groups of patients, and for what therapeutic objectives. Surveys using nationally representative samples of physicians, of course, provide the most reliable estimates of these prescribing patterns, but cannot detail the specific circumstances of individual patients who receive these prescriptions. There is more opportunity to gather detail relevant to individual cases in surveys of prescriptions issued by physicians in a given region, or within a specific practice or group of practices, and these data can be compared with the national-sample data for evaluation of the extent to which they are representative of the national population, or to which they reflect regional or practice-related variations; in any case, where these surveys do attempt to link prescriptions with other medical data on the patients receiving them, they have the potential to elaborate our picture of the circumstances in which these prescriptions are issued.

Both the national and other physician and prescription surveys present data that bear on the overall appropriateness of benzodiazepine prescribing. An important limitation of all of these studies, however, is that basically they examine only individual patient visits at which drug prescriptions are written; so even those studies that attempt to link prescriptions with patients' medical records generally provide little or no information about patients' medical histories, including patterns of drug use. This also limits the extent to which these data generally can be interpreted as bearing on the question of appropriateness.

Data of this kind have also stimulated considerable interest among medical sociologists and others in the possibility of distinguishing the specific social and medical determinants of prescribing of benzodiazepines and other psychoactive medications, including characteristics of the prescriber, the patient, the clinical setting, and the broader social context of medical care. A large num-

ber of studies have been published on these questions, which remain for the most part speculative and/or controversial. It would not serve the aims of this review to consider this literature in detail. However, a selection of references has been provided for the interested reader (23, 197, 50, 1113, 199, 193, 326, 798, 901, 39, 652, 196, 195, 291, 154).

1. Surveys of physicians. a. NATIONAL SURVEYS. **i. United States.** The National Disease and Therapeutic Index (NDTI) is an ongoing survey of a nationally representative sample of United States physicians in private practice; the survey is conducted by IMS America (Ambler, PA). The physicians are asked to record all drug prescriptions, and some characteristics of the patients receiving these prescriptions, for 2 days each quarter. Since physicians record their prescriptions by the specific products ordered, and since the NDTI reports do not combine the data on brand and generic versions of individual agents, the discussion of individual agents below refers to the brand-name products; the generic versions were prescribed in relatively small numbers. Benzodiazepines indicated as anxiolytics and as hypnotics are considered separately.

We examined the NDTI data presenting aggregate numbers for the benzodiazepine tranquilizers as a group for the 12 mo ending March 1986; we also compared these with equivalent data for the previous 4 yr, i.e., beginning with the data for April 1981, in order to note any indications of changes in prescribing patterns. Of all patient visits at which a benzodiazepine tranquilizer was prescribed, 85% were visits by patients who had been seen previously by the prescriber; 69% of all prescriptions were for patients who had previously received a prescription for the same medication from the same prescriber. These rates were virtually unchanged between 1981 and 1986. Unfortunately, it is not possible to draw inferences from these data regarding the duration of each prescription before the patient gets a "new" one.

Certain other data for the 12 mo ending in March 1986 represented some shifts in the patterns evidenced for the preceding 4 yr. The total number of prescriptions for benzodiazepine tranquilizers increased by 27% over this period. In 1985–1986, psychiatrists wrote 23% of all prescriptions for these agents; this represents a slight increase over the 5-yr period, up from 19% for the year ending March 1982; throughout the 5-yr period, about half of all prescriptions were written by primary care physicians (general practitioners, family physicians, and internists). The percentage of prescriptions for these drugs provided in physicians' private offices increased over the period from 59 to 66%; the percentage provided by telephone also increased, from 10 to 15%; while the percentage provided in hospitals decreased, from 28 to 18%. In 1985–86, slightly more than half (54%) of benzodiazepine tranquilizer prescriptions were issued to patients with diagnoses of mental disorders, including anxiety reactions in 24% and neurotic depressive reaction in 11%; each of these diagnostic categories represented increases over the 1981–82 figures, which were: all mental diagnoses, 45%; anxiety reaction, 18%; and neurotic depressive reaction, 9%. Other diagnostic categories accounting for substantial proportions of benzodiazepine prescriptions were circulatory disorders and ill-defined symptoms and senility. The physicians reported that they prescribed these drugs for the purpose of reducing anxiety or tension, etc., in 72% of cases and to promote sleep in 5%; these proportions were virtually unchanged from 1981 to 1986. Prescriptions for the purpose of skeletal muscle relaxation decreased over this period, from 8 to 5%, while prescriptions for antidepressant action increased from 2 to 6%.

A comparison of these data for the benzodiazepine tranquilizers with equivalent NDTI data for all prescription drugs reveals a few interesting points. Benzodiazepine tranquilizers were less frequently written on patients' first visits to the prescribing physician than were all prescriptions (15 versus 25%). Also, benzodiazepine prescriptions more frequently represented continued (as opposed to new) therapy than did all prescriptions (69 versus 55%).

The highest volume of prescriptions of oral benzodiazepine tranquilizers, in order of relative volume, was for Valium (diazepam), Xanax (alprazolam), Ativan (lorazepam), Tranxene (clorazepate), Librium (chlordiazepoxide), Serax (oxazepam), and Centrax (prazepam). Examination of the NDTI data indicates that, in most respects, prescribing of the individual agents closely paralleled prescribing for the drugs as a group, with the following notable exceptions: Librium (chlordiazepoxide) was prescribed more frequently than other benzodiazepines for patients with diagnoses related to alcoholism (20%) and was prescribed specifically for treatment of withdrawal symptoms in 11% of cases. Valium (diazepam) was relatively more frequently prescribed by surgeons and less frequently by psychiatrists than was the group of drugs considered together; it was prescribed less frequently for patients with mental diagnoses and was more frequently intended as a skeletal muscle relaxant. An unusually large proportion of prescriptions for Xanax (alprazolam) was written by psychiatrists and for patients with mental diagnoses, of whom a relatively high proportion had diagnoses of neurotic depressive reaction; accordingly, a relatively high percentage of prescriptions was intended as antidepressants.

Of the three benzodiazepines indicated for treatment of sleep disturbances, according to NDTI data for April 1985 through March 1986, the most frequently prescribed was Dalmane (flurazepam), followed by Halcion (triazolam) and Restoril (temazepam). The prescription profile of these drugs in general differed from that of the benzodiazepine tranquilizers, reflecting their frequent use as hypnotics both in outpatient therapy and following surgery. Of the three, Dalmane (flurazepam) was prescribed least frequently by primary care physicians and most

frequently by surgeons; accordingly, it was prescribed most often in hospitals and for surgical aftercare. Halcion (triazolam) was prescribed equally frequently for diagnoses of surgical aftercare and mental disorders. Of these three hypnotics, Restoril (temazepam) was prescribed least frequently by surgeons, and most frequently by primary care physicians and psychiatrists; it was least often prescribed for diagnoses of surgical aftercare and most often for mental disorders, including neurotic depressive reaction.

The National Ambulatory Medical Care Survey (NAMCS) is a survey of a national sample of United States physicians in private office practice, which is conducted by the U.S. National Center for Health Statistics. The survey was conducted annually until 1981, and beginning in 1985 was to be conducted every third year. Physicians record information about every patient visit during 1 wk in the year; the information includes data about the patient, symptoms, diagnoses, treatments ordered, disposition, etc. Beginning with the 1980 survey, physicians were asked to report drugs prescribed by name of the individual products specified. The most recent NAMCS data that have been analyzed are those for 1981.

The findings of this survey indicate that 2.4% of all visits to private physicians in 1981 were by patients presenting symptoms referable to psychological or mental disorders; mental disorders accounted for the principal diagnosis at 4% of all visits, making this the fourth most common principal diagnosis category, and neurotic disorders were among the most common principal diagnoses (1.6% of visits) (639).

An analysis by Koch and Campbell (588), in which 1980 and 1981 NAMCS data were combined, found that psychotropic drugs were prescribed at about 6% of all visits, or at 10% of visits where any medication was prescribed. Benzodiazepines accounted for 46.5% of all psychotropics prescribed. The specific benzodiazepines most commonly prescribed, in order of frequency, were Valium (diazepam, accounting for 15.8% of all psychotropic drug prescriptions), Dalmane (flurazepam, 5.3%), Tranxene (clorazepate, 4.6%), Ativan (lorazepam, 3.9%), Librium (chlordiazepoxide, 3.7%), Centrax (prazepam, 1.4%), and Serax (oxazepam, 1.2%); Limbitrol, a combination of chlordiazepoxide and amitriptyline, accounted for another 2.1% of psychotropic prescriptions. Psychotropics in general, and especially anxiolytics, sedatives, and hypnotics, were prescribed most frequently at visits where the diagnoses were in the following categories (using the WHO's International Classification of Diseases, ed. 9): mental disorders; symptoms, signs, and ill-defined conditions; diseases of the circulatory system; diseases of the digestive system; and diseases of the musculoskeletal system. These findings regarding the diagnoses for which these agents are most frequently prescribed accord with the NDTI data described above. Also in accord with NDTI findings, primary care physicians were responsible for the greatest proportion of prescriptions for anxiolytics and hypnotics—in this survey, 66%, which is considerably higher than the proportion found in NDTI for a comparable time period; since the NAMCS sample included a slightly higher percentage of primary care physicians than the NDTI sample, the explanation for this discrepancy is not apparent.

Koch and Campbell further found (588) that, especially with respect to anxiolytics, sedatives, hypnotics, and antidepressants, psychotropics were prescribed for females much more often than for male patients; this sex difference appeared only in the age ranges above 45 yr. The investigators noted that this disparity correlated positively with the diagnostic data, in that the conditions for which psychotropics were most commonly prescribed were diagnosed in older females proportionately more often than in males. They also found, again in parallel with the NDTI survey, that psychotropics were prescribed much more frequently for patients whom the prescriber had seen previously than for new patients, and moreover that these drugs were prescribed much more frequently for treatment of previously diagnosed problems than for new problems. The authors interpreted these findings as evidence of conservatism, which they felt was also manifest in the finding that patients receiving psychotropic prescriptions, on average, were much more frequently instructed to return at a specified time than were other patients.

The high proportion of psychotropic prescriptions that are written by primary care physicians motivated a separate analysis of the 1980 NAMCS data by Jencks (528). He found that, in more than half (58%) of visits at which psychotropics were prescribed, no mental diagnosis was recorded—which is consistent with NDTI data for a comparable period; this was especially true of visits with prescriptions for sedative tranquilizers (62%) and for hypnotics (73%). The investigator cited a number of previous studies providing evidence that mental problems are often recognized and managed in instances where no mental diagnosis is made. He also pointed out that the preponderance of cases where psychotropics are prescribed in the absence of a mental diagnosis are those of older patients with chronic disorders; this he found consistent with hypotheses that "either (1) treatments are provided for conditions incidental to other chronic somatic disorders and therefore are not separately diagnosed, or (2) mental treatments are provided for chronic mental conditions that are not recorded on every visit."

ii. Australia. Rowe (944) and Bridges (132) have reported analyses of data covering 1970 through 1974 from the Australian General Morbidity and Prescribing Survey, in which a nationally representative sample of general practitioners recorded data on all drug prescriptions for 1 or 2 wk each yr. During this period, barbiturates decreased from 6.6 to 2.9% of all prescriptions, while benzodiazepines increased from 1.9 to 4.6%. In 1974, the majority of benzodiazepine prescriptions were written for patients whose primary diagnoses were of

mental disorders, chiefly anxiety neuroses and transient situational disturbances; 37% were written for management of anxiety secondary to various physical disorders, chiefly hypertension, heart disease, migraine, arthritis, and duodenal ulcer.

b. OTHER PHYSICIAN SURVEYS. The national-sample physician surveys described above clearly show that, at least in the United States, the largest proportion of prescriptions for psychotropic medications in general, and especially of prescriptions for benzodiazepines, is issued by primary care physicians. Appropriately, most physician surveys concerned specifically with psychotropic prescribing have focused on general practitioners and family physicians.

One study that focused on the management of psychiatric disorders by primary care physicians was a postal survey conducted between August 1980 and February 1981 by Orleans and coworkers (829). The 610 physicians asked to participate were family practitioners selected by a random procedure from files of the American Medical Association; of these, 350 returned usable questionnaires. The respondents were not asked to provide data on specific cases, but to describe the psychiatric disorders they encountered in their practice and their characteristic treatment approaches. The physicians surveyed estimated on average that 23% of their adult patients had significant psychiatric problems warranting treatment, including most frequently anxiety and tension states, depression, alcohol abuse, sexual problems, psychophysiological and pain disorders, and adjustment reactions. They estimated that 57% of the psychiatric problems they saw were associated with physical illnesses. The physicians reported that in 45% of such cases they managed these problems with a combination of verbal therapy and psychotropic medication; 21% were treated with medication alone. Seven % of the respondents reported that they prescribed anxiolytics very frequently; 26.5% frequently; 42% fairly often; and 25% never or rarely. Only 1% reported prescribing sedative-hypnotics very frequently; 6% frequently; 29% fairly often; and 64% never or rarely.

The physicians surveyed in this study (829) were also asked to select from a prepared list the major obstacles they faced in providing psychiatric treatment or making appropriate referrals. The investigators found that "about two-thirds . . . reported that their patients resisted psychiatric diagnosis, treatment, or referral, but a similar proportion noted that they themselves had too little time to treat psychiatric disorders effectively. About one-third noted inadequate insurance reimbursement for mental health service, lack of coordination of primary care and mental health care, and limited training. . . ." These responses provide at least some rough insight into the reasons that most patients with mental problems present these problems to primary care physicians, and why they present them only to primary care physicians even when such problems are recurrent or chronic; they also clearly indicate that primary care physicians feel limited in their ability to provide appropriate care for these problems.

In 1971, Hemminki (454) sent a questionnaire to a "systematic sample" of 100 general practitioners in Finland, asking them to provide information on every patient visit on a designated day; 47 physicians agreed to participate. Eleven % of the diagnoses reported related to psychological disturbances and "obscure functional conditions," while psychotropic medications (including combination products with psychoactive ingredients) were prescribed for 21% of all conditions diagnosed. Diazepam was prescribed in 7% of all cases and other minor tranquilizers in 13%. Psychological and functional disorders were diagnosed most commonly in the age group of 35 to 49 yr. Although these diagnoses were made more commonly in women than in men, men received psychotropic prescriptions much more frequently than women; this finding is at variance with most evidence regarding sex differences in psychotropic prescribing (e.g., the NAMCS data discussed above), which indicates that women receive proportionately more prescriptions than men. More than half (57%) of psychotropic prescriptions were for somatic diseases; 20% were for psychic disorders. The investigator examined these data with respect to two hypotheses regarding the prescription of psychotropic drugs, i.e., that psychotropics are largely prescribed for somatic diseases, and that they are largely prescribed for "non-medical" problems; she concluded that the study findings supported the former and not the latter hypothesis.

2. Surveys of prescriptions. This section considers studies of prescriptions that have been written but not necessarily filled; studies of prescriptions sold are discussed in section V C above. Many surveys of prescriptions, or prescription records, have provided information on the use of benzodiazepines and other medications in various types of medical practice. These include chiefly surveys of outpatient treatment, based on records of individual and group practices as well as of outpatient programs of medical centers and hospitals, and some surveys of records of inpatient treatment.

The following section does not attempt to summarize the findings of these surveys with regard to extent of drug use, which is better addressed by the physician surveys reviewed above, and particularly by the household surveys described in section V E below. Rather, it focuses on the information pertinent to appropriateness of use, an issue which these prescription surveys do help to illuminate. The section first considers surveys of treatment provided for nonpsychiatric patients and then studies specifically of psychiatric patients; within each of these subsections, outpatient and inpatient studies are considered separately.

a. TREATMENT FOR NONPSYCHIATRIC OUTPATIENTS. There have been numerous surveys of prescriptions, issued in various medical practice settings to outpatients, which have provided data on the relative frequency of

prescriptions for psychotropics, in some cases specifying rates for minor tranquilizers, hypnotics, or specific benzodiazepines. Illustrative of these studies are the following publications, for surveys in the U.S. (1006, 461, 922, 1132, 673, 969, 438, 993, 792); in Canada (16, 936, 937); in the United Kingdom (1040, 1138, 68, 705, 1143, 1015); in Sweden (66); in Denmark (617); in Iceland (402); in France (429); and in Czechoslovakia (1042, 1044, 1116, 695). Some of these studies specifically address questions of the appropriateness of psychoactive drug use; these are discussed below.

Rickels and Hesbacher (922) studied prescribing patterns of seven family practices treating 172 patients who were found by their physicians to be experiencing emotional problems. Of 39 patients diagnosed as having anxiety states, the family practitioners prescribed minor tranquilizers for 34, antidepressants for 3, and antipsychotics for 2. Of 80 patients with mixed anxiety and depression, 49 received minor tranquilizers, 18 antipsychotics, and 13 antidepressants. Antianxiety agents were also prescribed for 22 of 32 patients with other emotional disorders (primarily "psychophysiologic"), and for 7 of 21 patients with depression. The authors' conclusion was that "... rational and appropriate psychotropic drug prescription can be achieved by interested family physicians."

The family practitioners described in this report (922) were part of a research group in which psychiatrists collaborated with family physicians in studies of the safety and efficacy of psychotherapeutic drugs. As part of this collaboration, the family physicians received training in diagnosis and treatment of emotional problems. As the authors noted, therefore, one should be careful about generalizing from the results of this study. On the other hand, it is interesting and encouraging that the authors felt that this type of training might be effective in improving the abilities of family physicians to diagnose and treat emotional problems appropriately (see discussion in "Summary and Discussion" below).

A study of the appropriateness of the use of diazepam, using a "case-control" design, was conducted in a primary care outpatient clinic by Mulvihill et al. (792). An independent research team reviewed the records of all patients who received prescriptions for diazepam between December 1979 and February 1980, as well as records of the patient seen by the same physician immediately before and the patient seen immediately after the diazepam "case"; these "controls" excluded patients who received a prescription for another benzodiazepine (and substituted others for those excluded). There were 101 "cases" (and 202 controls). The research team, which was blinded with respect to the identity of the prescribing physician and to the cases versus controls, reviewed the progress notes made by the physicians relative to both the case and the control patients, judged whether these notes described the presence of anxiety, and on this basis rated the appropriateness of a prescription for diazepam for each patient. It was found that neurotic disorders were diagnosed in 45.5% of the patients receiving diazepam and in 11.4% of the controls; also, musculoskeletal and circulatory diagnoses were more frequent among the diazepam group. However, only 30.8% of the patients who received diazepam prescriptions were judged appropriate candidates for such prescriptions by the research team, whereas 12% of those who did not receive diazepam were also judged appropriate candidates for diazepam on the basis of the physicians' progress notes. With respect to the large proportion of diazepam prescriptions that were not explained by the progress notes examined, the investigators noted that this study "was confined to the progress note made on a single visit, and the rationale or justification for a diazepam prescription may have been made during an earlier visit. . . ." This comment, which may in part explain the high proportion of prescriptions judged inappropriate, is consistent with data from the national-sample physician surveys described above (section V D 1 a), which indicate that about 85% of prescriptions for benzodiazepine anxiolytics are dispensed at visits by patients seen previously by the prescriber, and that mental diagnoses are made at a relatively small proportion of visits where such prescriptions are written.

Many of the medical practice surveys have found that older patients more frequently receive prescriptions for benzodiazepines and other psychoactive drugs than younger patients. A few of these studies have specifically examined the dosages and durations of psychotropic prescriptions for older versus younger patients.

A relatively early and particularly interesting study of this kind was reported by Parish (848), who had noted a "phenomenal" increase in prescribing of hypnotics and minor tranquilizers between 1965 and 1970 in the United Kingdom, and who sought to examine the ways in which these drugs were being used by conducting a retrospective survey of the prescribing patterns of a group of general practitioners. He examined the records of all prescriptions written from May 1967 through April 1968 by 48 physicians practicing in a Midland industrial city; records of patients less than 15 yr of age were excluded. Of the total of 13,259 patients whose records were examined, 12.6% (17.1% of females and 8% of males) received a psychotropic prescription during the year of the survey; older patients were overrepresented among those who received hypnotics (chiefly methaqualone-diphenhydramine and nitrazepam), while the age distribution was more even for patients receiving tranquilizers (chiefly diazepam and chlordiazepoxide). Parish estimated that the duration of continuous psychotropic therapy (based on frequency of prescriptions for individual agents for individual patients) was less than 1 mo in 57.8% of all patients receiving any psychotropic, 1 to 3 mo in 6.3%, 3 to 6 mo in 8.9%, 6 to 12 mo in 12.1%, 1 to 3 yr in 8.4%, and over 3 yr in 6.5%. Of those who were on medication continuously for a year or longer, 54% were women and 60.5% were at least 50 yr of age. Of the various types of

medications prescribed, barbiturate hypnotics tended to be the most likely to be used continuously for long periods. Parish also noted a positive association between duration of continuous therapy and the incidence of prescription records made by ancillary staff rather than the physicians themselves, indicating that long-term regular users were more likely than others to receive their prescriptions by requesting repeat prescriptions without direct contact with the physician.

Similar findings with respect to long-term regular use of psychotropics were reported by Dennis (222), who examined repeat prescriptions for psychotropics in 13 general practices in Bath, Cirencester, and Swindon (United Kingdom); the survey was conducted over a 2-wk period in 1979. In this period, a total of 1,031 such prescriptions were issued without direct contact between the patient and practitioner. The average age of the patients receiving repeat prescriptions was 58; the report did not state the average age of the entire patient population covered by these practices, nor of all patients receiving any psychotropic or other prescriptions. However, the investigator found that the duration of regular psychotropic use increased with the patients' age. Also, the length of time elapsed since the patient had last seen the physician increased with the duration of regular use. Among these patients receiving repeat prescriptions, the duration of psychotropic use was 1 to 3 yr in 45.6%, 3 to 10 yr in 40.6%, and 10 or more yr in 9.7%. The average age of those who had been taking these medications for 10 or more yr was 65. Benzodiazepines accounted for two-thirds of the repeat prescriptions issued; the report did not state how this proportion compared with that for the total practice population.

In a 1-yr (1977–1978) survey of prescriptions of diazepam, chlordiazepoxide, and flurazepam in a Canadian family medicine center, Rosser (936) found that 50.9% of diazepam prescriptions for patients over 65 were for 3 mo or longer, as opposed to 12.9% for younger patients; 36.5% of diazepam prescriptions for older patients were for more than 6 mo, as opposed to 3.2% for younger patients. Also, the daily dosage of diazepam prescribed for patients over 65 was only slightly lower than the dosage prescribed for younger patients (9.9 versus 11.9 mg/day). It might be noted that these are relatively low daily doses in any case.

Hasday and Karch (438) surveyed benzodiazepine prescribing in a U.S. family medicine center between July 1976 and June 1978. They found that the frequency of prescriptions for these drugs increased with age, up to the age of 64, after which the curve declined slightly. Patients aged 65 and older tended to receive prescriptions specifying lower daily dosages than did younger patients; among patients 65 and over, the median daily dosage for men was 15 mg and for women was 6 mg. Also, they found that the durations of benzodiazepine prescriptions tended to increase with age.

Weintraub et al. (1132) examined hypnotic prescriptions written by a number of family physicians between May 1974 and May 1975. They found that older patients were more frequently given hypnotic prescriptions than younger patients. Most (77%) hypnotic prescriptions were for flurazepam. The investigators found that, with respect to the number of flurazepam capsules prescribed and the provision of refills, prescribing for older patients was generally conservative; however, the data indicated that physicians did not prescribe lower daily dosages for older patients than for younger patients.

b. TREATMENT FOR NONPSYCHIATRIC INPATIENTS. Although the NDTI survey data described above (section V D 1 a) indicate that the percentage of benzodiazepine tranquilizer prescriptions issued in hospitals has decreased in recent years, these drugs continue to account for a significant proportion of all prescriptions for inpatients; benzodiazepine hypnotics also enjoy very extensive use in hospitals, e.g., for surgical aftercare.

Studies of inpatient drug treatment including the use of benzodiazepines have generally utilized hospital pharmacy records or other prescription records. Hospital surveys providing data on benzodiazepines have included studies of individual hospitals as well as studies of multiple hospitals, among which various parameters of drug use have been compared. Most of these studies have described the extent of use of psychotropics in the institutions surveyed; some have also explored questions of appropriateness of such prescriptions, relative to dosages used, use with other drugs, diagnostic categories, etc.

i. Cross-national studies. The Boston Collaborative Drug Surveillance Program monitors hospital drug use in several countries. Miller (766) reported an analysis of the data that had been collected in nine hospitals as of the beginning of 1972; these included data on a total of 11,526 patients monitored in six hospitals in the U.S., two in Canada, and one in Israel. The ten most common indications for drug therapy included insomnia (9.3% of all drug exposures) and anxiety (4.0%). Tabulation of the 15 most frequently prescribed drugs showed that chlordiazepoxide had been prescribed for 19% of U.S. patients and for 14% of Canadian patients; diazepam had been prescribed for 37% of Canadian patients and 29% of Israeli patients; and nitrazepam had been prescribed for 22% of Israeli patients.

Lawson and Jick (641) reported a study of data collected in this program on drug prescribing in eight U.S. and two Scottish university teaching hospitals; these two countries were selected for comparison because, of the countries monitored, they represented the highest (U.S.) and lowest (Scotland) overall rates of inpatient drug use. The data examined pertained to 1,442 U.S. patients and 721 Scottish patients hospitalized between 1972 and 1974; the Scottish and American patients were matched with regard to age, sex, and illness and hospitalization variables. For all diagnoses, American patients received an average of 9.4 drugs, as opposed to an average of 4.5 drugs per Scottish patient. Among patients with anxiety,

30% of the American patients and 20% of the Scottish patients received at least one drug prescription for treatment of that condition; 12% of the Americans and 14% of the Scots treated for anxiety received two or more drugs for this condition. The drugs most frequently prescribed for these patients were diazepam (63% of anxious patients receiving anxiolytics in the U.S. and 43% in Scotland); chlordiazepoxide (16% in U.S. and 2% in Scotland); phenobarbital (8% in U.S. and 20% in Scotland); chlorpromazine (2% in U.S. and 16% in Scotland); and promazine (none in U.S. and 13% in Scotland). Considering the variables that may have accounted for the differences found between the Scottish and U.S. prescriptions overall, the investigators concluded that "a major proportion of the difference appears likely to be due to physician prescribing habits rather than patient attributes."

ii. United States. In two studies (732, 217), the investigators reviewed the charts of hospital inpatients who had received prescriptions for diazepam or chlordiazepoxide. These studies found that the prescribing physicians' progress notes were generally inadequate and did not reflect clinical observations compatible with the drug treatment.

Salzman (962) studied records of drug prescriptions to determine what drugs were received on a randomly chosen weekday by all inpatients of a general hospital, excluding patients of the psychiatric service, the diabetic treatment unit, and the cardiac care unit. The date of the survey was not reported (but must have predated May 1979, when the paper was originally presented). Of the 348 medical and surgical inpatients surveyed, 42.8% were found to have taken a psychotropic drug on the survey day; the most commonly prescribed hypnotic was flurazepam (31.6% of all patients), and the most commonly prescribed nonhypnotic was diazepam (14% of all patients). All patients receiving a psychotropic were also taking at least one other medication; the mean number of drugs taken for the day by patients under 60 was 7.6, and the mean number for patients over 60 was 8.0. Of patients receiving flurazepam, 37% also received diazepam and another 11% received barbiturate hypnotics. The investigator noted that, while the amount of polypharmacy observed was not surprising in view of the severity of illness of most of the patients surveyed, some of the drugs prescribed for individual patients might be expected to interact adversely.

As reflected in the surveys described above, hospital surveys of drug use confront a number of methodological problems inherent in the hospital setting, which have generally limited the usefulness of such studies. These problems have been discussed by Prien et al. (891), who also described a design that would be more productive of meaningful data. These authors reviewed three multihospital surveys, each of which found evidence of overprescription and inappropriate prescribing of psychotherapeutic drugs. The reviewers criticized these surveys on a number of grounds: the surveys condemned treatment practices without taking into account the individual circumstances that might have justified such practices; they tended to rely on data collected from a single day or other brief period, which might have been misleading; they sometimes employed questionable standards for evaluating the appropriateness of dosage and other treatment variables; they did not attempt to verify the accuracy of diagnosis or to establish the relationship of diagnosis with drug therapy; and they failed to take account of the possibility that physicians may have had to make treatment decisions in situations not covered by conventional guidelines. The authors stressed the need for carefully planned longitudinal surveys that could focus on "long-term treatment strategies and reasons for treatment for a carefully selected, well-defined population."

iii. United Kingdom. Johnson and Clift (537) had surveyed general practice patients and found that, of those who had been taking hypnotics regularly on a chronic basis, 22% had begun taking these medications during a hospital stay. In order to explore the likelihood that a considerable proportion of such long-term hypnotic use begins in hospitals, they examined the prescription records of 143 consecutive patients discharged from the psychiatric, medical, and surgical units of the Manchester Royal Infirmary between October and December of 1966. They also examined the medical records of those patients who were referred back to their general practitioners following discharge, and who continued to receive hypnotic medications. The type of hypnotic prescribed was not specified, but on the basis of other sources regarding hypnotic use in the United Kingdom at the time of this study (e.g., ref. 848), the hypnotics prescribed might have included barbiturates, Mandrax (methaqualone-diphenhydramine), and nitrazepam. The study found that 86% of psychiatric patients, 58% of medical patients, and 32% of surgical patients had received hypnotics during their hospital stays. Of the 39 psychiatric patients who had received hypnotics as inpatients, 26 (67%) continued to receive them following discharge, of whom 20 were available for followup. Nine of these 20 were still receiving hypnotics at followup 18 mo later, of whom the medications were considered a necessary part of treatment for psychotic disorders in 4; the remaining 5 patients had been taking hypnotics when they were admitted to the hospital. Thus, the investigators considered that "no new cases of drug dependence developed from this small sample." Of the 9 medical patients who continued to receive hypnotics after discharge and who could be followed up, 2 were still taking these drugs at followup; the investigators noted that in both of these cases a psychiatric diagnosis had been made during hospitalization, in addition to the medical diagnosis made upon admission. Only 3 surgical patients continued to receive hypnotics following discharge, of whom 2 could be followed up; one of these was still taking hypnotics 18 mo after discharge.

Kesson et al. (575) found that, of medical inpatients

of the Glasgow Royal Infirmary during 1972–1973, 32% received a benzodiazepine during their hospital stay, and that a large proportion of patients receiving benzodiazepines received more than one benzodiazepine and/or other psychoactive agents as well. Smith et al. (1024) compared psychotropic drug use in medical inpatients of the Glasgow Western Infirmary between 1973 and 1975 with that between 1982 and 1983; they found that psychotropic prescriptions during hospitalization decreased over this time period, as did the percentage of patients receiving two or more psychotropic drugs concomitantly (from 23 to 14%).

iv. Other countries. Surveys of prescriptions issued in hospitals in several European countries in the 1970s indicated that 37% of medical inpatients in a Finnish hospital received prescriptions for diazepam during hospitalization (844); prescriptions for anxiolytics, sedatives, or hypnotics were issued to 43% of medical inpatients in Sweden, mostly for insomnia (65), and to 68% of surgical patients in Northern Ireland (203); and that 27% of inpatients of a number of small hospitals in northern Norway received prescriptions for nightly use of hypnotics (909).

A study of prescriptions issued in three major hospitals in Bangkok, Thailand, in 1980–1982 found that 15% of all prescriptions for outpatients and 25% of all prescriptions for inpatients were for benzodiazepines (582).

c. TREATMENT OF PSYCHIATRIC OUTPATIENTS. It is clear from the research described previously that most patients with emotional problems seek help from primary care physicians and that numerous obstacles to formal mental health care (e.g., see ref. 829) usually limit the treatment of these problems to that provided in primary care. Thus, it may be assumed that patients treated by psychiatrists generally have more severe and/or more chronic emotional disorders, that have overcome these obstacles to psychiatric care.

Anxiolytics (chiefly bromazepam and lorazepam) accounted for 21.5% of all prescriptions, and hypnotics (chiefly flunitrazepam and flurazepam) accounted for another 24.5% of prescriptions provided in a Swiss psychiatric outpatient clinic in 1981 (985). A lower rate of prescriptions for minor tranquilizers was found in 1980 in another Swiss psychiatric outpatient clinic, probably because this was a university clinic, with younger patients (53).

Some studies of prescriptions used in treatment of psychiatric outpatients have focused on the extent of concurrent prescriptions for multiple psychoactive drugs and on the extent of long-term prescriptions issued to these patients. For example, Fritz et al. (322) found that, of adult psychiatric outpatients seen at a California community mental health center in 1975, 55% of patients receiving prescriptions for minor tranquilizers had also received prescriptions for concurrent use of other psychoactive drugs; the types of these other drugs were not specified.

Kass et al. (568) conducted a quality review of outpatient psychopharmacological practice, based on screening criteria for further review as proposed by a task force of the American Psychiatric Association (245). They studied records of treatment of 180 outpatients of a psychiatric clinic of a teaching hospital in New York City; the patients were randomly selected from among those receiving each of six categories of psychoactive medications, including antianxiety and hypnotic agents (not broken down by specific drugs). Prescriptions for antianxiety drugs met several of the criteria for further review, including: duration longer than 3 mo (83% of all cases); uncommon indications (33%); use with an antipsychotic (27%); and use with more than one other psychotropic drug of any class (13%). Prescriptions for hypnotics met the following criteria for further review: duration longer than 7 consecutive days (73% of cases); use with more than one other psychotropic drug of any class (20%); and history of addiction to sedatives/hypnotics (20%). The authors noted that the most common questionable practice found in this outpatient study, i.e., continued prescription of drugs over excessive periods of time, contrasted with the most common questionable practices found in surveys of prescribing for psychiatric inpatients, namely, concurrent prescriptions for multiple psychoactive drugs and excessive doses.

Hemminki (456) examined the records of prescriptions on a single day in 1976 for a sample of 694 patients representing all psychiatric inpatients and outpatients in Helsinki, Finland. Sixty-nine % of the patients received two or more psychotropic drugs on the day of the survey. Antianxiety agents (types not specified) were used in combination with antipsychotics in 6% of the cases and in combination with antidepressants in 2%. Hypnotics were used in combination with antipsychotics in 6%.

d. TREATMENT OF PSYCHIATRIC INPATIENTS. Hubbard and Kripke (499) reported a study of unusual design and of particular interest in connection with assessment of the influence of hospital drug use on subsequent use, and on the risks of abuse and dependence, among the general population. The investigators cited previous authors who had questioned whether hospital use of hypnotics, in particular, might be a significant factor leading to abuse of these agents following discharge. They undertook a study of 109 admissions to the psychiatric inpatient service of a university-affiliated Veterans Administration hospital during a 5-mo period in 1972. They examined the medical charts on these patients for data on duration of hospitalization and on both inpatient and outpatient use of hypnotics and minor tranquilizers. The outpatient prescription information was checked against pharmacy records, which were verified in turn by telephone contact with a subgroup of the sample after discharge. The mean time of followup was 8.2 mo after discharge. The investigators noted that the only hypnotics used by this service were flurazepam and chloral hydrate; they did not specify what minor tranquilizers were used.

They found (499) that the incidence of use of hypnotics

among these patients following discharge was consistent with previously reported statistics (706) on the extent of hypnotic use for the population of this area (California); and that patients who had received hypnotics as inpatients were not significantly more likely to use them as outpatients than those who had not received hypnotics as inpatients. However, patients who had received minor tranquilizers during their hospital stay were significantly more likely to use them as outpatients than those who had not received these medications as inpatients; this association was not related to the dosage of minor tranquilizers given to the patients during hospitalization. The investigators noted that their study lacked the design and control features that would have made it possible to infer a causal relationship from the observed association between inpatient and outpatient drug use. In addition, they pointed out that a strong association should be expected between inpatient and outpatient use of given drugs among the same individuals, on the basis that these individuals' medical needs are likely to remain the same after discharge: "Such an association was observed with minor tranquilizers, and although this association raises the concern of habituation, it does not demonstrate it." It might also be noted that the investigators apparently did not examine what drugs these patients might have been receiving at or prior to the time of their admission to the hospital, which might have influenced the choice of treatments ordered for them as inpatients. Despite these deficiencies, nevertheless, this study admirably addressed an issue of compelling and possibly far-reaching concern; unfortunately, the further exploration of this issue which the authors urged has apparently not been pursued.

Swett (1066) reported a study of drugs prescribed for 2,592 psychiatric inpatients monitored over a 6-yr period (dates not specified) in six hospitals (in Boston, MA; Miami, FL; Minneapolis, MN; New York, NY; and Helsinki, Finland). Diazepam had been prescribed for 16.1% of all patients, chlordiazepoxide for 7.6%, and flurazepam for 5.3%. The benzodiazepines were not among the drugs associated with a high frequency of adverse reactions.

Winstead et al. (1160) found that minor tranquilizers were prescribed for 16 to 38% of the patients of the acute short-stay psychiatric units of five hospitals in a midwestern U.S. city. Seventy % of the patients received concurrent prescriptions for three or more drugs, usually including hypnotics.

Other studies providing information about the use of benzodiazepines in psychiatric inpatients include a survey of prescribing in four Missouri state psychiatric hospitals (11), a survey of prescriptions for psychiatric patients admitted to a Saskatchewan university hospital (320), and a study of prescriptions in a child psychiatric facility in Manitoba (7).

3. Summary and discussion. a. PHYSICIAN SURVEYS. Data from surveys of nationally projectable samples of U.S. physicians indicate that most prescriptions for benzodiazepine anxiolytics and hypnotics are issued to patients previously seen by the prescribing physician and represent continued therapy for problems previously treated by the physician. Benzodiazepine prescriptions are considerably more likely than most other drug prescriptions to have these characteristics. These data reflect the fact that the use of benzodiazepines is chronic or recurrent in a substantial majority of cases. They are probably also an indication of conservatism on the part of physicians, who rarely prescribe these medications for new patients; physicians prescribing benzodiazepines (and other psychotropics) are also especially likely to instruct these patients to return at a specified time, which suggests that they may be particularly concerned to monitor the progress of patients receiving these drugs.

About half of the patients receiving prescriptions for benzodiazepine tranquilizers have primary diagnoses of mental disorders. The remainder of these prescriptions are for patients whose primary diagnoses relate to a wide variety of somatic disorders, especially circulatory, digestive, and musculoskeletal problems, as well as "symptoms, signs, and ill-defined conditions." (The finding that a substantial proportion of prescriptions for anxiolytics and hypnotics is written for patients whose primary diagnoses are of somatic disorders was also reported based on roughly comaprable physician surveys conducted in 1970 and 1971 in Australia and Finland.)

Half or more of all benzodiazepine anxiolytic prescriptions are written by primary care physicians. Of the remainder, the greatest proportions are written by surgeons and psychiatrists.

These characteristics of prescriptions for benzodiazepine anxiolytics are roughly shared by the benzodiazepine hypnotics, except that a greater proportion of these are prescribed by surgeons for surgical aftercare.

Use of benzodiazepine anxiolytics and hypnotics increases sharply with age up to about age 65, after which there is a slight decline. Above the age of 45, women receive nearly twice as many prescriptions for these drugs as men do; this appears consistent with sex differences in relevant symptoms and diagnoses.

In sum, these data indicate that medical use of benzodiazepine anxiolytics and hypnotics is generally consistent with what is known about the clinical utility of these medications; there is no evidence, at least in these data, that there is frequent inappropriate prescribing of these drugs. These data also suggest that the patient who receives an anxiolytic prescription is typically an older person, probably female, who is afflicted by multiple somatic health problems.

b. PRESCRIPTION SURVEYS. As opposed to the physician surveys summarized above, which provide data pertaining to drug prescriptions based on individual patient visits, many of the prescription surveys provide more detail about the prescriptions themselves and about the overall therapeutic regimens in which these prescriptions play a part. It is of interest to learn, for example, that

older patients tend to get prescriptions for longer periods of anxiolytic or hypnotic medication than do younger patients. Some interpretations of this finding, however, have failed to take into account that, based on national-sample data, this practice in general may be explained by the chronic nature of the somatic disorders characterizing older benzodiazepine users (and especially long-term users, as described in section V E 4 below). Another finding of some prescription surveys is that benzodiazepine prescriptions for older patients call for daily doses equal to, or slightly less than, those prescribed for younger patients; in studies reporting this finding, however, the doses described tend to fall toward the low end of the recommended range in any case. It might be noted that analysis of NDTI data indicated that a national sample of U.S. physicians tended to prescribe lower doses of benzodiazepine anxiolytics and hypnotics for patients 65 and older, as compared to younger patients (545).

There is some information, particularly from surveys of prescriptions for medical inpatients, regarding other drugs administered concurrently with benzodiazepines. It has been reported occasionally that a substantial proportion of hospital patients receives prescriptions for more than one benzodiazepine daily, e.g., an anxiolytic for daytime use as well as a hypnotic. The available information suggests that the extent and pattern of this use vary considerably among institutions and among individual prescribers. However, this information does draw attention to a seemingly questionable practice, which deserves further investigation.

There have been relatively few surveys of prescriptions specifically for psychiatric patients, but the evidence available at least from studies in the U.S. is fairly consistent. This evidence suggests that about one in four psychiatric outpatients as well as inpatients receives a prescription for a benzodiazepine anxiolytic. Psychiatric patients who receive prescriptions for benzodiazepine anxiolytics or hypnotics are likely to continue to receive such prescriptions for relatively long periods of use and are also likely (especially if they are inpatients) to receive concurrent prescriptions for neuroleptics or other psychoactive agents.

A substantial proportion of anxiolytic prescriptions, and especially of hypnotic prescriptions, is provided in hospitals. Some authors have expressed concern that hospital prescribing of these agents may be responsible for initiating a substantial proportion of the long-term use and possible abuse of these drugs. The information available to date on hospital prescribing of benzodiazepines is inadequate as a basis for evaluation of this important possibility. To arrive at a reasonable estimate of the general significance of hospital use of psychotropics, it will be necessary to undertake the considerable effort and expense of prospective longitudinal studies of use of these medications by clearly characterized samples of hospital patients before, during, and after hospitalization.

Large-sample surveys, such as the national physician surveys described above, can address the question of the general appropriateness of medical use of benzodiazepines (or other medications), in that they depict associations between drug prescriptions and diagnoses and other relevant clinical variables. Such studies do not, however, address the issue of the accuracy and quality of the diagnostic procedure itself, an issue that seems especially important in that, as these large-scale studies indicate, the majority of benzodiazepine prescriptions are written by primary care physicians without extensive formal training in diagnosis of emotional problems presented as primary or as secondary to somatic disorders. This issue has been addressed to some extent in some of the smaller-scale prescription surveys, in which it has been possible to link prescription records to medical records and physicians' progress notes detailing diagnostic and therapeutic variables pertinent to individual cases. However, the relevant findings of these studies are inconclusive.

Some investigators have found that physicians' progress notes and other patient records do not include reasons for prescribing anxiolytic medications, nor report on the effectiveness of these agents, even when the same physicians' records appear quite detailed and clear about other types of conditions and drug treatments. In some studies, this has been interpreted as evidence that, because of inadequate knowledge regarding diagnosis of emotional problems and about the use of psychoactive medications, physicians tend to overprescribe them or to prescribe them inappropriately, thus increasing the risks of abuse and dependence. Other investigators interpret such findings differently, suggesting that primary care physicians may accurately detect and appropriately manage emotional problems, although they may not record such problems as distinct diagnoses. This view seems more consistent with several documented factors. Most patients receiving these prescriptions are patients who have previously consulted the physician, and who are receiving treatment for chronic or recurrent conditions; so that a sample of the physician's notes about any given visit is unlikely to register specific attention to a chronic emotional problem. Also, and perhaps more importantly, a substantial proportion of anxiolytic prescriptions is for anxiety accompanying or secondary to somatic illness, and physicians (particularly those in primary care) may concentrate on the latter. Indeed, they may do so in part because somatic disorders are more amenable to objective evaluation by measures in whose use they have been trained.

Thus, prescription surveys that have attempted to judge the appropriateness of benzodiazepine prescriptions on the basis of physicians' records from a single patient visit, or another limited period of patient contact, have tended to fail to take into account both the chronicity and the somatic nature of the diagnoses preponderant among these patients. Such studies have therefore

adequately addressed neither the appropriateness of these prescriptions nor the quality of the diagnostic procedures which motivate these prescriptions.

Most patients who seek help for emotional problems present these problems in one way or another to primary care physicians and only to primary care physicians. This is reflected in the surveys summarized here; the reasons for this phenomenon, and the strong probability that this will continue to be the case for the foreseeable future, have been documented in numerous studies focusing on the social and economic barriers to formal mental health care (e.g., see ref. 1114). Meanwhile, the best available evidence indicates that primary care physicians generally prescribe benzodiazepines appropriately; and some information (e.g., ref. 922) encourages the thought that primary care physicians have the ability to increase their skills in diagnosing and treating emotional problems. This represents a critically important opportunity for improving the effectiveness of care available for emotional disturbance. To take advantage of this opportunity, research must be undertaken systematically to provide more information about how emotional problems are presented to physicians; how physicians assess these symptoms and how this assessment can be improved; how primary care physicians approach treatment of emotional problems in different kinds of patients and circumstances; and what kinds of information might help them to select and prescribe psychoactive medications more effectively and with least attendant risk.

E. Surveys of Consumption

Surveys of consumption, in which members of the community or of some defined population are questioned about their use of medications, provide the epidemiological data of most direct relevance to the assessment of the abuse liability of benzodiazepines. In part, this is because this is the only significant source of information, not only as to how people actually use these medications, but even as to whether they use them at all. It is known that a small percentage of prescriptions for these drugs, as for other drugs as well, is not filled (262); the literature is replete with evidence that a considerably greater proportion of prescriptions is filled but not used, or only partially used, due in large part to "undercompliance" (e.g., ref. 500), but also in some instances to apparent hoarding (e.g., ref. 262).

The importance of community surveys as a complement to prescription studies was especially well illustrated by Hulka et al. (500, 501), who compared medical records of prescriptions with information on actual use of these prescriptions obtained in household interviews. The study measured four types of discrepancies between prescriptions and actual compliance patterns, i.e., drugs prescribed but not taken; drugs taken but not prescribed; drugs for which the patient did not know the prescribed dose and/or frequency of administration; and drugs for which the patient knew but did not comply with the prescribed dose and/or frequency. Of all categories of medications prescribed, only drugs acting on the CNS (chiefly tranquilizers) scored significantly higher than average for all four of these types of discrepancies. This category also had the highest score with respect to drugs for which the patients knew but did not comply with the prescribed dose and/or frequency; the nature of this noncompliance was indicated by the finding that the category also scored significantly above the average with respect to the proportion of drugs prescribed but not taken, i.e., patients did not use the drugs or used less than prescribed. These findings clearly suggest that, while prescription data may provide important information about the clinical context in which drugs are prescribed and about the characteristics of patients for whom these prescriptions are written, they may be a particularly inadequate indicator of the actual consumption of psychoactive medications.

Among those who do use these medications, only survey research provides significant information about patterns of use—how frequently they take the drugs; how much they take in a day, week, or month; for what periods of time they use the drugs on an intermittent or regular basis; etc. This information is centrally relevant to the assessment of the drugs' abuse liability.

Apart from these data on whether and how people actually use benzodiazepines, community surveys also provide information bearing on the appropriateness of use that is at least as important as medical records of those patients receiving prescriptions for these drugs. These surveys alone offer a picture of populations in which it is possible to see how many of those afflicted by various morbid conditions are in fact using medications indicated for treatment of these conditions, and conversely how many of those using various drugs are afflicted by ailments for which those drugs are medically indicated. Further, they provide by far the greatest wealth of detail regarding the demographic, socioeconomic, cultural, and health-care characteristics of benzodiazepine users.

The following review considers survey research on the use of benzodiazepines in order of the scope of the populations surveyed: cross-national studies; national studies; and regional and other studies. Data from these studies on individual patterns of use, as well as studies specifically focused on patterns of use, are considered separately.

A number of hypotheses have been derived from or offered as explanations of these data. This review will focus on data and hypotheses of particular relevance to assessment of the abuse liability of benzodiazepines, including data that address the question of appropriateness of actual use of the drugs and data that illuminate patterns of individual use.

A number of interview surveys, as well as studies with other types of design, have focused on determinants of benzodiazepine use other than the psychiatric and medical conditions for which these drugs are indicated. These

so-called "nonspecific" factors leading to or affecting benzodiazepine use include attitudes toward the use of tranquilizers, perceived health, peer influence, use of other prescribed or nonprescribed drugs, socioeconomic factors, sex, age, health behavior (including frequency of medical consulting), etc. It would not serve the interests of this review to consider these studies in detail. However, a number of selected references have been provided for the interested reader (217, 1149, 53, 775, 891, 709, 844, 922, 962, 732, 432, 7, 757, 894, 194, 653, 618, 483, 66, 193, 414, 945, 223, 453, 460, 552, 902, 168, 455, 594, 673, 708, 730, 767, 765, 764, 848, 1010, 1053, 162, 215, 651, 734, 791, 899, 1027, 513, 580, 528, 1146, 1132, 198, 993).

1. Cross-national surveys. a. WHO INTERNATIONAL COLLABORATIVE STUDY OF MEDICAL CARE UTILIZATION. A standardized instrument was used in 1968–1969 to gather information on rates of use of prescribed and nonprescribed medications in twelve study areas, representing seven countries, participating in the WHO International Collaborative Study of Medical Care Utilization (592). Survey respondents were interviewed in their homes about use of medications on the day of interview and the preceding day. Among adults surveyed, 33.9% of women and 18.7% of men reported use of some prescribed medication during the 2-day period; this sex difference was similar across the countries surveyed. Use of prescribed minor tranquilizers was reported by a mean of 1.9% of adults in the seven countries (United Kingdom, 1.2%; Canada, 1.3%; Poland, 1.5%; Finland, 1.6%; Yugoslavia, 2.0%; U.S., 2.2%; Argentina, 3.4%). It should be noted that, depending on the country involved, the category of minor tranquilizers at the time of the survey would have included nonbenzodiazepines, e.g., meprobamate, hydroxyzine, phenobarbital, etc., as well as the benzodiazepines chlordiazepoxide, diazepam, and lorazepam.

b. NIMH CROSS-NATIONAL SURVEYS. There have been two formal household surveys that have focused on the use of anxiolytic drugs across countries. Both were sponsored by the U.S. National Institute of Mental Health and were conducted by Balter and coworkers. Questions were developed based on the investigators' experience in regional and national surveys in the United States (which are described in section V E, 2 and 3, below). Identical sets of questions were used in household interviews of national samples of the adult populations of the countries surveyed. In the first study (41), conducted in 1971, the countries surveyed were Spain, Italy, the Netherlands, Germany, Great Britain, Denmark, Sweden, France, and Belgium. A similar study (42), conducted 10 yr later in 1981, surveyed these same nine Western European countries as well as Switzerland and the United States. In both surveys, respondents were asked about their use of any psychoactive medications during the preceding 12 mo; the data used were those pertaining only to the use of drugs indicated for the management of anxiety and tension states, i.e., minor tranquilizers and sedatives (both barbiturate and nonbarbiturate) but excluding hypnotics and other types of psychoactive medication. Although respondents were apparently questioned about specific drugs used, the reports do not provide a breakdown by individual compounds.

These surveys found that, on average for the countries surveyed, the 12-mo prevalence of anxiolytic use was about 14% in 1971 and 12.5% in 1981. The prevalence data reported for the individual countries appear in table 19, which ranks the countries studied in 1971 in order of the prevalence of use found at that time. (The table also shows an estimate of prevalence for the U.S. in 1971, based on a national survey conducted at that time by the same set of investigators.)

Although the findings of these surveys are reviewed here together, it is important to consider at least two caveats about direct comparisons. (*a*) The investigators in the more recent report (42) point out that, although the two surveys used basically similar methods, they differ in several important respects (which, however, were not specified). (*b*) Even if it is appropriate to consider the differences between the 1971 and 1981 data as representing change, neither the overall change nor the changes within countries should be construed as unilinear. Pharmaceutical marketing data indicate that anxiolytic use in the U.S. increased from 1970 to 1975 and decreased from 1975 to 1980 (899); similar curves appear to have characterized use in at least some of the other countries surveyed as well, though in varying time frames (see the "Summary and Discussion" of section V C, pages 333 and 334).

Nevertheless, the prevalence rates found in the two surveys, as shown in table 19, do indicate certain consistent patterns. At both time points, the highest prevalence of anxiolytic use was found in Belgium and France. Use declined in most countries, especially in Sweden and the Netherlands, which in 1981 showed the lowest rates of use. Only in Spain was there an apparent substantial increase in use prevalence between 1971 and 1981.

In both surveys, use was substantially higher for

TABLE 19

Twelve-month prevalence of use of antianxiety/sedative drugs (percentage of population)

Country	1971*	1981†
Belgium	16.8	17.6
France	16.7	15.9
Sweden	15.8	8.6
Denmark	15.1	11.9
Great Britain	14.2	11.2
Germany	14.2	11.3
Netherlands	12.7	7.4
Italy	11.2	11.5
Spain	9.7	14.2
Switzerland		14.6
United States	15‡	12.9

* Based on Balter et al. (41).
† Based on Balter et al. (42).
‡ Based on Parry et al. (851).

women than men in every country. This difference, which was apparent within almost all age categories, is consistent with the great majority of physician and prescription surveys, as well as of national and regional interview surveys described in the following sections, that have considered sex differences in prescribing and use of minor tranquilizers. In most countries, use prevalence was much higher in persons aged 35 or older than in younger age groups; in the U.S. and Switzerland, however, at least in 1981, rates were more equal among the young, middle, and older age groups.

These surveys also provided information on patterns of use of anxiolytic medications. These data are considered in section V E 4 below.

2. National surveys—United States. Apart from the cross-national studies discussed above, the United States is the only country for which data on the use of psychoactive drugs are available based on interviews of samples representative of the national population. Two of these surveys were sponsored by the National Institute of Mental Health (NIMH) and conducted, in 1970–1971 and 1979, respectively, by the same group of investigators responsible for the NIMH-sponsored cross-national surveys described above. A third survey providing information on use of psychotropic drugs in the U.S. was the National Medical Care Expenditure Survey, sponsored by the National Center for Health Services Research (NCHSR).

a. NIMH SURVEYS. In the survey conducted in 1970–1971, Parry et al. (851) found that 15% of U.S. adults had used a minor tranquilizer or daytime sedative in the 12 mo preceding the interview; since the investigators noted that 80% of this drug use consisted of the use of minor tranquilizers (chlordiazepoxide, diazepam, and oxazepam, as well as nonbenzodiazepine minor tranquilizers), this puts the 12-mo prevalence of use of minor tranquilizers at 12%. This finding would indicate that prevalence of use of these drugs in the U.S. at the time of the survey was within the range found for the nine Western European studies surveyed in 1971 (cf. table 19 above). Also consistent with findings of the cross-national surveys, twice as many women as men reported use of antianxiety drugs; and use was found to increase with age. The characterization of use by women in this report is particularly interesting, in that there was little variation in use by women across socioeconomic classes, except that women in the lowest social position and with the least education were the most likely to use anxiolytics regularly for 2 mo or longer. The study also found that people living in the western U.S. were somewhat more likely than those in other regions to use prescription anxiolytics or sedatives, and that they were also more likely to have obtained these drugs through nonmedical channels; people living in the West, however, as the investigators pointed out, were also somewhat more likely than others to report high levels of psychic and somatic distress.

A further analysis (754) of the data from this survey considered the relationship of use of psychotropic medication to levels of psychic distress and life crises. Psychic distress was rated using an adapted version of a scale conventionally used in drug studies, the Hopkins Symptom Checklist (HSC). (To establish the validity of the findings of this survey, with respect to the appropriateness of drug use, the investigators compared the HSC data for the high-distress survey respondents with HSC data on more than 1,000 anxious-neurotic outpatients who had been evaluated by psychiatrists as part of multiclinic drug studies and for whom drug therapy had been deemed appropriate.) In addition, the number and severity of life crises of survey respondents were measured using an adapted version of a standard scale for rating stressful life events, the Holmes-Rahe "social readjustment rating scale." As noted above, minor tranquilizers accounted for about 80% of the psychotropic drug use reported. In this report, users of these drugs were considered in two groups. "Users" were those who had used a psychotropic drug in the 12 mo prior to the interview, and "regular users" were those who had used a psychotropic drug in the prior 12 mo and who at any time had used the same drug daily or almost daily for 2 mo or longer.

The investigators found that 27% of American adults reported that they had experienced high levels of psychic distress during the year prior to the interview; high distress was more prevalent among women (34%) than among men (19%). One-third of the sample reported high levels of life crises in the prior year. Among those with high levels of psychic distress, 30% were psychotropic "users," and 12% were "regular users"; among those with low psychic distress, 8% were users, and 3% regular users. Thus, conversely, the prevalence of untreated psychic distress was 70%; of those with high levels of psychic distress, of life crises, or both, 65% of women and 79% of men had not used a psychotropic drug during the previous 12 mo. The authors further noted that somatic conditions might have accounted for a substantial proportion of the reported psychotropic use among those who did not have high distress scores.

The 1979 NIMH survey employed basically the same methods as those used in the 1970–1971 survey. The later survey found (756) that 11% of adults in the U.S. had used some anxiolytic medication during the 12 mo prior to interview. This figure can be compared with the 12% of the population found to have used a minor tranquilizer in the year prior to the 1970–1971 survey. However, as the investigators pointed out in another report (752), prescription sales data indicate that minor tranquilizer sales increased to a peak volume in 1973 and declined thereafter, so that the roughly equivalent levels of use found in the 1970–1971 survey and in the 1979 survey should not be interpreted as evidence that there was no change in the extent of use over this period. Benzodiazepines accounted for 84% of the anxiolytic use found in

the 1979 survey, so that the 1-yr prevalence of use of benzodiazepine tranquilizers among American adults in 1979 was about 9%.

As in the earlier study, the 1979 data indicated (756) that most people who used anxiolytics actually took these medications only occasionally; 45% reported never taking the drugs for more than a day or two at a time, and more than 80% of these occasional users had taken the drugs on fewer than 30 days during the prior year. However, 15% of all those reporting use (i.e., 1.6% of the total adult population) reported that they had used the same anxiolytic agent regularly for 12 mo or more. (These data on patterns of use, as reported in this and other reports of the 1970–1971 and the 1979 surveys, are considered in more detail in section V E 4 below.) As compared with nonusers, anxiolytic users tended to be older, to have experienced higher levels of psychological distress and impairment, to have had more somatic health problems, and to have made more frequent visits to physicians; also, a greater proportion of users than of nonusers was female.

Another report (752) of the 1979 survey indicated that 14.4% of all women in the U.S. and 7.5% of men reported having used an anxiolytic in the prior year. Anxiolytics were the most widely used of all psychotropic drugs; the second most widely used group was hypnotics, which were used by 3% of women and 2.1% of men. Among age groups, the prevalence of use of anxiolytics was highest among those 50 to 64 yr of age and declined slightly for older respondents; use of hypnotics was most prevalent among those aged 65 to 79. Respondents were also asked about use of prescription drugs that they obtained by means other than prescriptions, e.g., from a relative or friend, etc. The pattern of such nonmedical drug use paralleled medical drug use, in that anxiolytics were the most frequently used and hypnotics the next most frequently used of the groups of psychotropics in nonmedical use. Anxiolytics were used without prescriptions by 2.3% of women and by 2% of men; 0.4% of women and 0.9% of men reported nonmedical use of hypnotics during the previous year.

In this report (752), the investigators described some general comparisons between the findings of the 1970–1971 and the 1979 surveys. Data from these two time points revealed no important changes in the prevalence of use of the various types of psychotherapeutic agents, except for a slight decline in the use of hypnotics and of daytime sedatives. Both studies found that physicians were generally conservative in their practices of prescribing psychotropic drugs, and that the public tended to report negative attitudes toward use of these medications in general, associated with conservative attitudes toward how these drugs should be used; the 1979 study yielded evidence that this general conservatism, on the part of both physicians and the public, had increased from the time of the earlier study.

Uhlenhuth et al. (1100) analyzed the 1979 survey data pertaining specifically to anxiety syndromes and their treatment. Since the survey instrument included a slightly modified version of the HSCL, it was possible to identify persons in the general population with certain clinical syndromes that could be correlated with standard psychiatric diagnostic criteria, as defined in the current (third) edition of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM-III, ref. 13). In DSM-III classifications, the survey found that the 1-yr prevalence of agoraphobia/panic syndromes was 1.2%; of other phobias, 2.3%; and of generalized anxiety syndromes, 6.4%. As the investigators noted, these rates of anxiety disorders are somewhat lower than might be inferred from the experience of clinical practice. All three of these anxiety syndromes were more prevalent among women than among men; generalized anxiety syndromes afflicted 4.3% of men and 8% of women. The prevalence of agoraphobia/panic and generalized anxiety syndromes increased with age, whereas other phobias were more common among those under 35. Of those with agoraphobia/panic syndromes, 55% reported having used an anxiolytic medication during the prior year, as did 12% of those with other phobias and 27% of those with generalized anxiety syndromes. The investigators concluded that "the majority of respondents with these anxiety syndromes do not receive psychotropic agents or those agents currently regarded as the treatments of choice." They also pointed out that even fewer respondents sought out or received psychiatric or other psychosocial help for these problems, so that "... upwards of 40% received neither pharmacological nor psychosocial treatments."

One analysis (757) of the 1979 survey data focused on insomnia and its treatment. The study found that 35% of adults in the U.S. in 1979 had trouble falling asleep or staying asleep, or both, within the previous 12 mo. Insomnia was classified as "serious" in 17% of the population. Women were more likely than men to report insomnia during the prior year. The data indicated that 4.3% of the population had used some prescription medication to promote sleep during the previous year. Of those with serious insomnia, 10% had used some prescription medication, as had 5% of those with less serious sleeping problems. The investigators noted that, even taking the use of over-the-counter (OTC) sleeping pills into account, 85% of those with serious insomnia reported taking no medication to promote sleep. Prescription drugs specifically indicated for the treatment of insomnia, i.e., hypnotics, were used by 2.4% (2.1% of men and 3.0% of women) of the population in 1979. This use of prescribed hypnotics represents a decline from the 1970–1971 survey, which showed a rate of use of prescription hypnotics of 3.5%; the authors noted that this evidence of a decrease was consistent with data from the National Prescription Audit (cf. section V C 2 b above), which indicate that the numbers of hypnotic prescriptions filled in U.S. drugstores declined from 42 million in 1971 to 21 million

in 1982. Other drugs used to promote sleep in 1979 included medications indicated for treatment of anxiety (used to promote sleep by 1.2% of the population; 1.6% of females and 0.6% of males) and OTC hypnotics (used by 3.1% of the populations; 3.1% of females and 3.0% of males). It seems worth noting that, unlike the findings for medically prescribed drugs, there was virtually no sex difference in use of OTC sleeping pills. This recalls the hypothesis, regarding the sex differences in reporting psychological problems (and in seeking and receiving medical care for such problems), that men may be underreporting such problems, because of social stigmata selectively affecting men or for other reasons; it is of interest that men will apparently use medications for sleep problems as often as women will, if they can get them without having to go through medical or psychiatric channels.

b. NCHSR SURVEY—NMCES. The National Medical Care Expenditure Survey (NMCES) consisted of six rounds of interviews during 1977 and 1978 with each of about 14,000 randomly selected households representative of the noninstitutionalized population of the U.S. (152). This survey collected data on all age groups, including children, so that the figures obtained for extent of drug use are predictably lower than those obtained in the NIMH surveys described above, which refer only to use among adults between 18 and 79 yr of age. The NMCES survey found that 9.1% of the total U.S. population received a prescription for one or more psychotropic drugs in 1977. Females of every age group were almost twice as likely as males to have used prescribed psychotropics. The prevalence of psychotropic use was found to vary inversely with years of schooling and family income; those with less than 12 yr of education had a prevalence rate of 14.4%, while those with 16 or more yr of schooling had a prevalence rate of 9.1%.

Anxiolytics accounted for 53.8% of all psychotropics prescribed for mental disorders and 65.7% of all psychotropics prescribed for circulatory disorders. The overall patterns of prevalence of anxiolytic use emerging from these data appear closely consistent with patterns revealed through physician and prescription surveys, as well as the national-sample NIMH surveys discussed above. One point on which these findings appear to vary pertains to the association between use and age. Whereas the NMCES data show that the prevalence of use of psychotropics in 1977 increased linearly with age, physician surveys (i.e., NAMCS; see pages 365 and 366) indicate that psychotropic use increases with age only up to the age of about 65, after which it slightly declines. The reasons for this difference in findings are not apparent.

3. Regional and other surveys. There have been numerous publications reporting interview surveys on the extent of consumption and other aspects of use of benzodiazepines within limited geographical areas and populations. Some of these studies have collected data on use of psychotropics in general; others have focused specifically on benzodiazepine use. Table 20 presents a description of an illustrative sample (certainly not an exhaustive listing) of these surveys. (There have also been a large number of studies of drug use among the youth of many areas of the world. In general, these data refer to nonmedical use; these studies are therefore briefly discussed under "Surveys of Misuse," in section V G 1 below.)

A few of the surveys described in table 20 include information relevant to the appropriateness of benzodiazepine use. These and several other studies of particular interest are reviewed in this section.

a. REGIONAL SURVEYS BEARING ON APPROPRIATENESS OF USE. In a survey conducted in 1970–71 in the city of Oakland, CA, Uhlenhuth et al. (1099) asked a sample of 735 noninstitutionalized adults about psychological problems, life events, and coping tactics including use of medications. Twelve % of men and 27% of women, or 20% of the total sample, reported having used minor tranquilizers or sedatives during the previous year; 10% had used such drugs daily for a week or more. More white than black respondents had used these medications; but there were no significant differences in rates of use associated with marital status, religion, or social class. These findings agreed with findings in the national study conducted by these investigators (851). Moreover, unlike the national study, the Oakland study found no differences in use according to age; the authors pointed out this was probably due to a localized phenomenon, namely, the relatively high rate of use among young people in the urban San Francisco Bay area.

An interesting focus of this study was the relation of data on use of psychoactive medication to emotional problems. Prevalence of use of minor tranquilizers was directly related to the amount of disturbance experienced, as measured in a variety of ways. Prevalence of use was also related to the type of disturbance reported; use of minor tranquilizers was highest among persons reporting psychological disturbance, and especially anxiety. Few people with no disturbance reported use of these drugs. On the other hand, the majority of persons reporting the highest levels of disturbance did not use psychoactive medications; thus, these findings are suggestive more of underutilization than of overutilization of these drugs. Finally, the study found that users of minor tranquilizers and sedatives tend to use these drugs as a part of a complex pattern of coping behaviors employed to deal with psychological distress.

Harris et al. (432) interviewed by mail every fifth patient, between the ages of 17 and 70, of a group practice in a rural area of Great Britain; the date of the survey was not reported, but from the publication date must have been before 1977. The medical records of 970 patients were examined to determine the use of psychoactive drugs at the time of the survey or during the preceding year. About 10% of the sample had received psychoactive prescriptions during the preceding year, including

TABLE 20
Regional and other surveys of consumption

Study	Characteristics and no. of patients	Area represented	Date of study	Period of use	Drugs	Parameters studied; special features
Vaillant et al., 1970 (1106)	45 physicians chosen from liberal arts colleges in 1930s	U.S.A.	1949; 1953; 1957; 1964; 1967	Ever used	Tranquilizers	
Sallis and Lichstein, 1982 (961)	2,460 adults, private houses, nationwide (1963); 1,441 community residents (1972); 1,010 community residents; various other populations	U.S.A., Canada, etc.	1963, 1972, etc.	(Not given)	Benzodiazepines; chlordiazepoxide	Anxiety; adverse reactions; drug interactions
Nora et al., 1967 (814)	240 mothers	U.S.A.: Houston, TX; Madison, WI		During term of pregnancy	Tranquilizers	Prenatal treatment
Manheimer et al., 1968 (706)	1,026, age 21 or over; noninstitutionalized	U.S.A.: nationwide	5/67, 6/67	Ever used; used frequently	Tranquilizers	Sex; age; marital status; race; religion; education; family income; occupation
Mellinger et al., 1971 (753)	1,104 age 18 or over; cross-section of noninstitutionalized residents	U.S.A.: San Francisco, CA	Fall 1967–winter 1968	Prior yr	Psychotropics; Rx* drugs; benzodiazepines; chlordiazepoxide; diazepam; oxazepam	Age; sex; regularity of use
Parry et al., 1971 (850)	900–1,200 over age 17	U.S.A.: midwestern city of 50,000	Winter 1968–spring 1969	Prior 6 mo; prior 2 yr	Sedatives; tranquilizers; psychotropics; Rx drugs	Admission of drug use
Blum et al., 1969 (93)	200 noninstitutionalized adults	U.S.A.: San Francisco Bay area, CA		Ever used; currently using	Psychotropics	Drug use behavior and attitudes
Hubbard and Kripke, 1976 (499)	109 of 114 admissions to psychiatry inpatient service; university-associated VA hospital	U.S.A.: La Jolla, CA	1972	(Not given)	Hypnotics; flurazapam; minor tranquilizers	Outpatient use
Greenblatt et al., 1975 (385)	24,633 nonpsychiatric inpatients, including 5,079 users	U.S.A.: Boston; 24 hospitals	1972	Prior 3 mo	Psychotropics; diazepam; chlordiazepoxide; barbiturates; meprobamate; oxazepam; flurazepam; antianxiety	Age; sex; diagnosis only by psychotropic
Ilfeld, 1978 (504)	2,299, age 18–64; respondents from 2,299 households	U.S.A.: Chicago, IL; northwest IN	Summer 1972	Prior wk	Psychotropics	Psychiatric symptoms; psychosomatic disorders; sex; age; marital status; race; income; education; occupation
Munson et al., 1980 (794)	3,839 age 18 or over; selected randomly from households drawn to be representative of each community	U.S.A.: Washington County, MD; Kansas City, MO	1972–1974	Probably currently using, but not clear	Psychotropics	Race; sex; age; marital status; income; education; reasons for taking drugs; sleep problems; depression; inability to "get going"

TABLE 20—*Continued*

Study	Characteristics and no. of patients	Area represented	Date of study	Period of use	Drugs	Parameters studied; special features
Craig and van Natta, 1978 (208)	771 men; 1,059 women from community	U.S.A.: Washington County, MD	1972–1974	Prior 2 days	Psychotropics	Depression; sex
Craig and van Natta, 1982 (208)	771 men; 1,059 women	U.S.A.: Washington County, MD; Kansas City, MO		Prior 2 days	Minor tranquilizers; combination tranquilizer depressants	Depression/drug use
Eve and Friedsam, 1981 (279)	8,061 Texans, age 60 or over	U.S.A.: TX	1974	Prior mo	Tranquilizers	Sex; marital status; race; employment; and many other variables
Bowker, 1976 (126)	516 adults; no method of selection described	U.S.A.: 2 rural communities; Pacific Northwest	1974	Once in prior yr; once per mo in prior yr; once per wk in prior yr	Rx drugs; tranquilizers	Attitudes toward drug use; parents' use; sex; age; health
Hulka et al., 1975 (501)	357 patients of various practices who had diabetes or congestive heart failure	U.S.A.: Fort Wayne, IN	(Not given)	Currently taking	Tranquilizers	Age; sex; education; social class; drug-use discrepancies; compliance
Fidell, 1977 (291)	465 females, age 20–59; English speaking	U.S.A.: San Fernando Valley, Los Angeles, CA	2/75; 2/76	Prior yr	Rx drugs; psychotropics; tranquilizers	Source of drugs; personality variables; many other variables
Shepherd et al., 1978 (1009)	614 middle-aged, middle-class FL women; major urban centers	U.S.A.: FL	6/75	Prior 2 yr	Rx drugs; tranquilizers	Abuse; misuse
Apsler and Blackman, 1979 (22)	1987, age 18 or over; random sample	U.S.A.: Boston, MA	1976	Prior several mo	Tranquilizers	Others' use
May et al., 1982 (731)	3,192 ambulatory elderly population	U.S.A.: Dunedin, FL	8/78–7/80	Daily, several times a wk; weekly; occasionally	Rx drugs; diazepam; flurazepam; meprobamate; chlordiazepoxide	Age; sex; duration of drug usage
Barsky et al., 1979 (50)	34 patients who were issued prescriptions for diazepam or chlordiazepoxide at neighborhood health center	U.S.A.: Boston, MA	(Not given)	(Not given)	Diazepam; chlordiazepoxide	Sex; age; social class; prior psychiatric contact; level of use; medical status; psychiatric status
Juergens et al., 1983 (546)	383 mothers and their 954 children under age 18 in rural areas	U.S.A.: Lee and Calhoun Counties, MS	2/80–1/81	Prior 2 wk	Rx drugs; psychotropics	Anxiety; anxiety/drug use; mother's anxiety/children's drug use
Radelet, 1981 (901)	181 of 200 from random sample of university student population	U.S.A.: Midwest	(Not given)	Prior 2 yr	Tranquilizers; diazepam; chlordiazepoxide; meprobamate	Sex; parents' education; parents' yearly income; anxiety; health perceptions; attitude toward drug use; parents' and friends' use

TABLE 20—*Continued*

Study	Characteristics and no. of patients	Area represented	Date of study	Period of use	Drugs	Parameters studied; special features
Keller et al., 1982 (572)	217 subjects; white; at least 17 yr of age; IQ at least 70; current episode of major depressive disorder of at least 1-mo duration	U.S.A: New York City; St. Louis; Boston; Iowa City; Chicago	(Not given)	Used during most recent depressive episode	Minor tranquilizers	
Chambers et al., (not dated) (161)	General population; 30,000, no method of selection described	U.S.A.: 16 states and DC; excludes West Coast	(Not given)	Prior 6 mo	Barbiturates; nonbarbiturates; sedatives; minor and major tranquilizers	Sex; age; social class; race; occupation; projection to national scale
Cooperstock, 1978 (195)	Province of Ontario, vital statistics 1973; Ontario insurance agency data 1970–71, 1973–74	Canada: Ontario	1970–1974	Not given	Psychotropics; tranquilizers; diazepam; chlordiazepoxide	Sex
Fejer et al., 1972 (287)	1,200 adults; randomly selected	Canada: Toronto	Spring 1971	Prior yr	Psychotropics; tranquilizers	Age; sex; multiple drug use; health; social characteristics
Chaiton et al., 1976 (159)	Random sample of households (n = 1,501); random sample of families attending a medical practice (n = 1,133)	Canada: Smithville; Burlington	1971–1972	Prior 2 days	Rx drugs; tranquilizers	Drug use in patients assigned to physician vs. drug use in patients assigned to nurse practitioner; change in drug use over time
Smart and Goodstadt, 1977 (1019)	1,015, age 18 or over; nationally representative	Canada: Ontario	1976	Prior yr	Tranquilizers	Sex; age; language; occupation; education; income; community size
Marinier et al., 1982 (711)	1,187 age 18–65; chosen according to level of drug use	Canada: Montreal	1979	Prior yr	Psychotropics; tranquilizers; diazepam	Sleep; anxiety; fatigue; nervousness; insomnia; tension; depression
Pihl et al., 1982 (871)	1,187 of random sample of 1,673 French-speaking women	Canada: Montreal	(Not given)	Prior yr; prior wk	Psychotropics	Age; health; happiness; diagnosed health problems
Lapp et al., 1982 (634)	180 women, age 18–65; randomly chosen from earlier study; French speaking	Canada: Montreal	(Not given)	Prior 2 mo; prior yr	Rx drugs; psychotropics; diazepam; chlordiazepoxide; lorazepam; oxazepam; flurazepam	Depression; problem solving
Lapp et al., 1983 (635)	179 women; French speaking	Canada: Montreal	(Not given)	Prior yr	Rx drugs; psychotropics; diazepam; flurazepam	Depression; anxiety; cognitive impairment
Stevenson and Gaskell, 1971 (1040)	78 general practice	United Kingdom: city not given	(Not given)	Ever used	Hypnotics	Age; drug use over time; reasons for use

TABLE 20—*Continued*

Study	Characteristics and no. of patients	Area represented	Date of study	Period of use	Drugs	Parameters studied; special features
Murray et al., 1981 (797)	5,904 of 8,510 selected from population	United Kingdom: West London	1977	Prior 2 wk	Psychotropics; tranquilizers	Health; sex; age
Anderson, 1980 (17)	836, age 18 and over; of 1000 from random sample	United Kingdom: England, Wales	3/77–7/77	Prior 2 wk	Rx drugs; psychotropics	Prescription data; sex; age; social class
Harris et al., 1977 (432)	727 patients from a group practice (every 5th patient from practice)	United Kingdom: city not given	(Not given)	Prior yr	Psychotropics	Age; sex; social class; tobacco; MHQ scores
Cummins et al., 1982 (212)	7,735 middle-aged males	United Kingdom: nationwide	(Not given)	Prior 2 days	Tranquilizers	Age; social class; health-illness(es); tobacco; alcohol; occupation
Murray et al., 1982 (798)	124 of 153 patients receiving psychotropic drugs from 6 general practitioners	United Kingdom: area not given	(Not given)	Prior 6 mo	Psychotropics	Age; marital status; household composition; employment
Cook et al., 1982 (190)	7735, age 40-59 males in British regional heart study	United Kingdom: nationwide	(Not given)	Not given	Tranquilizers	Age; health; marital status; tobacco; alcohol; employment
Pflanz et al., 1977 (868)	Random sample of 1,251 subjects born in 1920	West Germany	1970; 1972	Prior yr	Tranquilizers; oxazepam; diazepam; chlordiazepoxide	Perception of health; working conditions; origin; family; education; social class; sex; psychological symptoms; social aspects of medical use
Milner, 1969 (768)	564 psychiatric patients; 4,020 general practice patients	Australia: Perth	6/67–7/67	Currently using	Psychotropics; tranquilizers; chlordiazepoxide; diazepam; Rx drugs	Alcohol; driving
Bridges-Webb, 1972 (130)	346 from random sample	Australia: Traralgon	11/70–12/70	Prior 2 wk	Rx drugs	Age; reasons for use; source of drugs (doctor, self, chemist)
George, 1972 (346)	639 from random sample; age 14–65 yr	Australia: Sydney	7/71–8/71	Ever used	Sedatives; tranquilizers	Sources of drug knowledge; age; sex
George, 1972 (346)	639 of 279 households; random sample of residents of largely middle-class suburbs; age 14–65	Australia: Sydney		Ever used	Tranquilizers	Age; sex
Chapman, 1976 (164)	(unspecified)	Australia	1973–1975	Prior 2 yr	Tranquilizers	Age
Reynolds et al., 1976 (914)	8,516 adults	Australia: Sydney	6/75–12/75	Currently using	Sedatives; tranquilizers	Concomitant use of psychotropics and analgesics; concomitant use of alcohol and other drugs

TABLE 20—*Continued*

Study	Characteristics and no. of patients	Area represented	Date of study	Period of use	Drugs	Parameters studied; special features
Flight et al., 1983 (304)	311 of 339 consecutive hospital admissions; age 16 or over; maternity patients excluded	New Zealand: Northland	2/80–3/80	Currently using	Tranquilizers	Age

* Rx, prescription(s); MHQ_1, Middlesex Hospital Questionnaire.

3% who were taking these medications at the time of the survey. With respect to the previous-year prevalence of use, but not to current use, significantly more females than males were among the psychoactive users. For both sexes, both current and past-year use increased sharply with age. Of potential respondents to the mailed questionnaires, 82.5% responded. Data from these questionnaires, which included a standardized self-report scale for rating psychoneurotic morbidity (the Middlesex Hospital Questionnaire), revealed that psychoactive drug users of both sexes had significantly raised morbidity scores, especially reflecting anxiety and depression, in comparison with the respondents who had not received psychoactive prescriptions.

Tyrer (1094) reported a study of the drug treatments that had been prescribed by general practitioners for patients referred to a psychiatric outpatient clinic between January 1974 and December 1977; the study group included 287 patients referred by 80 general practitioners. The treatments that these patients were receiving at the time of their referral were recorded at their initial interview; the report did not specify whether this information was provided by the patients themselves or whether it may have been obtained from the referring physicians. Most of the patients were diagnosed as having neurotic disorders, chiefly depressive neuroses. The investigator assessed the suitability of the drug treatments these patients had been receiving, based on the length of treatment, the dosage prescribed, and the number of drugs with similar pharmacological actions that each patient was taking. He found that two-thirds of the 147 patients receiving benzodiazepines had been taking these drugs for more than 2 mo, although "long-term treatment with benzodiazepines . . . in regular dosage has no established value in psychiatric disorders." Of 158 patients taking benzodiazepines or barbiturates, five (3.2%) were regularly taking doses higher than the maximum recommended dose, i.e., 40 mg/day for diazepam or the equivalent for other drugs. Of patients who had been taking benzodiazepines, 20 (16%) had received concurrent prescriptions for two or more benzodiazepines or other drugs with similar pharmacological actions. Tyrer also noted that, of the 61 patients who had received regular psychotropic prescriptions for over a year, 20 had initially received prescriptions for these drugs in a psychiatric clinic or hospital, after which their general practitioners had "apparently continued these prescriptions regardless of whether regular treatment was indicated."

Pflanz et al. (868) surveyed a random sample of all people born in 1920 who lived in the city of Hannover, Federal Republic of Germany, in 1970; of the total sample of 2,000 people, 1,251 completed all three stages of the survey, which included a household interview, a medical examination (both conducted in 1970), and a mail questionnaire (in 1972). Regular use of some tranquilizer was reported by 14.7% of the male respondents and 27.1% of the females. Oxazepam, diazepam, and chlordiazepoxide accounted for half of this use. For male users, there was a significant association between social class (upper and upper-middle) and tranquilizer use; there was no such association for women. Analyses of a variety of other variables, reflecting work status, health behavior, indicators of "social stress," etc., showed few associations with tranquilizer use. However, responses to two standard psychiatric rating scales (the Midtown 22-Item Scale and the Psychiatric Symptoms Scale) showed a significant association between tranquilizer use and psychological and psychophysiological impairment; at the same time, an appreciable proportion of users had low scores on these scales. The investigators concluded that the data supported "a psychiatric-medical model [of tranquilizer use] rather than a sociological one."

Siciliani et al. (1011) studied the use of psychotropic drugs and the abuse of alcohol in a stratified probability sample of the residents of South Verona (Northern Italy). Use of psychotropics within the 2 wk prior to the survey, which was conducted in 1980, was reported by 18% of women and 9% of men. Benzodiazepines accounted for 70% of psychotropic use among women (yielding a 2-wk prevalence of use of 13%) and 85% of psychotropic use among men (for a prevalence of 8%); about half of this use was of benzodiazepine hypnotics. Minor psychiatric morbidity was measured using the Italian version of the General Health Questionnaire (GHQ). Twenty % of men and 30% of women who had high GHQ scores reported use of some psychotropic, as opposed to 7% of men and 12% of women who had low GHQ scores. Alcohol abuse (defined as "usual" consumption of at least 120 g per day) was reported by only one woman but by 22% of men. Among male alcohol abusers,

19% had low GHQ scores, and 40% had high GHQ scores; there was no association between alcohol abuse and psychotropic consumption. The authors commented that this finding was consistent with previous suggestions that distressed men are more likely to drink, while distressed women are more likely to use minor tranquilizers. Statistical analysis indicated that the greater prevalence of psychotropic use among women than among men was independent of the effects of both age and psychiatric morbidity. The authors noted that this finding, like the overall finding regarding prevalence of psychotropic use in this Northern Italian population, agreed closely with findings of a similar study conducted in West London (797).

It has been reported in a number of studies that depressed patients are treated with minor tranquilizers more frequently than with other psychoactive drugs, including antidepressants. Craig and van Natta have pointed out that this may represent an inappropriate pharmacological choice for treatment of depression and, moreover, that there is some evidence that benzodiazepines in high doses may produce depression in nondepressed persons. These investigators reported a study (209) relating medication use and depressive symptoms in the general community, that was undertaken as part of a larger interview survey sponsored by the U.S. NIMH and conducted in two regions of the U.S.—Washington County, MD, and Kansas City, MO. The sample for this study consisted of 1,830 respondents, who were asked about medication use during the previous 48 h and were administered a depression rating scale developed by the NIMH Center for Epidemiological Studies. The data indicated that 4.3% of men and 9.3% of women reported use of minor tranquilizers within the 48 h prior to interview; 2.5% of men and 3.3% of women had used sedatives during this period. Of all medication categories, only in these two categories did users have significantly higher depression scores than nonusers; these differences were significant only for women, although trends in the same direction were observed for men. As the authors pointed out, since this was a cross-sectional survey, it is not possible to infer from these data whether depressive symptoms led to use of tranquilizers and sedatives or whether use of these drugs led to depressive symptoms; however, because of the questions that have been raised about the efficacy and even the safety of using minor tranquilizers in treating depression, the observed association deserves further exploration.

Another study of medication use among depressed persons was reported by Keller et al. (572). Unlike the study by Craig and van Natta (209), described above, which identified persons in the general population with depressive symptoms, this study focused on persons who specifically met DSM-III criteria for major depressive disorder. The study sample was comprised of the first 217 subjects entered into the NIMH Collaborative Study of the Psychobiology of Depression, which was conducted at university medical centers in five cities in the northeastern and midwestern United States. Data pertaining to treatments these subjects were receiving at the time of entry into the study indicated that 67% were receiving psychotherapy, 55% were receiving antianxiety medication, and only 34% had been receiving antidepressant medication for at least 4 consecutive wk; 19% were taking anxiolytics but no other medication. The investigators felt that their most important finding was the low prevalence of use of antidepressant medications among these depressed patients; they discussed possible reasons for this, including the possibility that prescribing physicians may not sufficiently recognize depression and/or may not be sufficiently familiar with the usefulness of antidepressant drugs for this condition.

b. OTHER REGIONAL SURVEYS. A pretest of the methods used in the U.S. national-sample surveys described above (section V E 2) was carried out in California in 1967 (706). Roughly consistent with the findings of the national studies, this survey of 1,026 adults indicated that 19% had used a minor tranquilizer within the preceding year. The study report focused on "frequent" users, i.e., those who reported using psychoactive medications "regularly" or "fairly often"; the report did not indicate how the frequent users differed from other users. The study found a preponderance of women (14% of women had been frequent users versus 6% of men) among frequent users; they noted that this contrasts sharply with available evidence regarding the sex difference in consumption of alcohol. There was also an overrepresentation of those who were separated or divorced (27%). There was no significant difference among frequent users with respect to race, religion, income, or educational characteristics.

As part of the Boston Collaborative Drug Surveillance Program, in 1972, 24,633 patients were questioned on admission to Boston area hospitals about their prior use of psychoactive drugs (384); respondents were consecutive admissions to general medical and surgical wards, excluding psychiatric patients and patients whose diagnoses indicated typically psychogenic disorders. About one in five of these patients indicated that they had used psychoactive medications within the 3 mo prior to admission. Two-thirds of these, or 14% of all patients, had used anxiolytics; 11% had used benzodiazepine anxiolytic agents, including diazepam in 6.3% and chlordiazepoxide in 4.5%. Four % of the patients had used hypnotics, chiefly pentobarbital and secobarbital. The study found that "patients with certain potentially chronic diseases (neurologic disorders, musculoskeletal diseases, and ischemic heart disease) were more likely to use psychotropic drugs than the rest of the sample." Also, use was more prevalent in middle- and older-age groups, and among women.

Warheit et al. (1129) presented data on psychotropic

drug use collected (apparently in 1970) as part of a large-scale study of mental health needs and services in Alachua County, FL; the authors noted that this county was representative of "the new South . . . in a state of rapid transition from a traditional, rural, agricultural area to one characterized by an expanded economic base, a rural-urban shift, racial tensions, and institutional alterations." Respondents, interviewed in their homes, were 1,633 adults representative of the county's 1970 population. Questions about drug use asked about any kinds of prescribed or nonprescribed medication respondents had used previously or were using currently. The report presents the data on psychoactive drugs in categories such as "tranquilizers" and "sedatives," so that it is difficult to estimate the extent of use by more specific drug types. Some of the findings were nonetheless of interest: Of the 35% of respondents who had ever used tranquilizers, 17% reportedly used them "all the time or every day," while 9% used them "often," and 10% used them "rarely." Females, and particularly black females, were more likely to have used tranquilizers and sedatives than males. Extent of reported prior use of tranquilizers was inversely related to socioeconomic status. Reported prior use of sedatives increased with age, while reported prior use of tranquilizers peaked in the middle years (ages 45 to 59). The authors noted that their findings regarding extent of tranquilizer use were comparable to those reported in earlier studies.

The Epidemiological Catchment Area Program (ECA) is a series of five regional U.S. surveys, supported by the NIMH, which studies the prevalence of DSM-III psychiatric diagnoses and their treatment among the general population. Data from the first wave of interviews in the St. Louis (MO) ECA, conducted in 1980–1981, found that the 6-mo prevalence of use of diazepam among adults was 7.25%, while that of chlordiazepoxide was 2.61%, and that of flurazepam was 1.18%. The frequency of use of diazepam and chlordiazepoxide was significantly greater among women than men. Use of diazepam was most frequent among those aged 55 to 64, while use of flurazepam was most frequent among those 65 or older. An interesting aspect of this study was that respondents were questioned in two different ways about use of certain psychoactive medications. As in many previous household surveys (e.g., the cross-national and national-sample surveys conducted by Balter and coworkers, described in section V E, 1 and 2, above), respondents were asked "indication-specific" questions, such as: "During the last six months, . . . have you taken any medications to help you calm down or keep you from getting nervous or upset?" However, in this study, respondents were also asked "medication-specific" questions regarding the use of certain drugs whose trade names were considered likely to be familiar, such as: "In the past six months, . . . have you taken any Valium for any emotional problems . . .?" The addition of this medication-specific question increased the rates of reported use by 43% for both diazepam and chlordiazepoxide and by 35% for flurazepam (204, 205).

Fejer and Smart (286) reported data from surveys of psychoactive drug use among adults in metropolitan Toronto in 1971 and 1974. In 1971, 13% reported that they were currently using tranquilizers (the authors did not specify what the "tranquilizer" category included), while 19% reported current use of tranquilizers in 1974. Use by females was higher than among males at both time points and increased significantly more among women than men between 1971 and 1974. During the same period, use of barbiturates increased only slightly, from 9% to 10%. Rates of use did not vary significantly among age groups. Thirty-eight % of tranquilizer users in 1971 (4.8% of the total sample) and 27% in 1974 (5.1% of the sample) reported that they used these medications "almost daily."

A similar study was conducted among a representative sample of Ontario adults in 1976 (1019). During the preceding 12 mo, 13.6% (7.9% of men and 19.3% of women) had used tranquilizers (again, not further specified as to type), and 8.6% had used "sleeping pills" (not further specified). The study found that, while more females used these medications, more males reported use of alcohol and marijuana. Tranquilizer use was highest among people aged 30 to 49, while use of sleeping pills increased with age. Use of hypnotics but not tranquilizers varied inversely with income. In contrast with the findings of the 1971 and 1974 surveys reported by Fejer and Smart (286), regular use of tranquilizers was reported by only 10.3% of users in this study (2.6% of the total sample), while 41.6% of users (5.7% of the sample) used tranquilizers less than once a month.

4. Survey data on patterns of use. Information on the ways in which people actually consume benzodiazepines is of critical importance to assessment of their abuse liability. Comparison of the frequency and duration of actual use with the regimens prescribed may be suggestive of the drugs' abuse potential; in addition, information on the proportions of users with various patterns of use may be suggestive of the relative liability of the drugs to produce dependence in the general population of users and in subgroups that may be particularly susceptible to abuse and/or dependence.

The best available evidence of this kind comes from surveys in which users are questioned directly about their patterns of use. These include the cross-national surveys sponsored by the U.S. National Institute of Mental Health (discussed in section V E 1 above), as well as the U.S. national surveys also sponsored by the NIMH (discussed in section V E 2). In addition, several other community and medical practice surveys provide important information on patterns of use.

a. CROSS-NATIONAL DATA ON PATTERNS OF USE. As described previously (section V E 1), the 1971 cross-

national survey sponsored by the NIMH consisted of interviews with national samples of the adult populations of Spain, Italy, the Netherlands, Germany, Great Britain, Denmark, Sweden, France, and Belgium; the 1981 survey, with closely similar methods, gathered data from these same nine Western European nations as well as Switzerland and the United States. In the 1971 survey (41), depending on the country surveyed, between 30 and 64% of all users (3.4 to 8.1% of the total populations) reported having used anxiolytics regularly for at least 1 mo during the preceding year; the average was 46% of all users or 6.5% of the total populations surveyed. Users aged 45 or older, who were in general overrepresented relative to their share of the populations, were even more overrepresented among those who reported long-term regular use. In the 1981 survey (42), although most users in every country except Belgium reported regular use for less than a month during the preceding year, relatively high proportions of the populations reported daily anxiolytic use for 12 mo or more—ranging from 0.5% (Sweden) up to 5.8% of the entire adult population of Belgium. As seen in table 21, between 6.2 and 33.2% of all those who had used an anxiolytic drug during the preceding year reported daily use for 12 mo or longer; the average for such long-term use was 19% of all users for the 11 countries surveyed. The report of this 1981 survey provided no breakdown of duration of use by sex or age of respondents.

b. NATIONAL DATA ON PATTERNS OF USE. Data on patterns of use of prescribed anxiolytics and hypnotics, as well as on characteristics distinguishing those who report different patterns of use, were collected in both the 1970–1971 and the 1979 national-sample surveys of the U.S. sponsored by the NIMH. In the 1970–1971 survey (851), it was found that users of minor tranquilizers and sedatives were divided fairly equally among those who, over the previous year, had used the drugs on a daily basis for less than a week (and on fewer than a total of 31 days); those who had used them daily for at least a week but less than 2 mo; and those who had used them daily for at least 2 mo. Of these long-term regular users, 80% (or 4% of the total sample) reported daily use for 6 mo or longer. Although females were twice as likely as males to report that they had used these medications over the prior year, among users females and males were equally likely to report long-term daily use.

TABLE 21

Duration of regular daily use of antianxiety/sedative drugs in 1981 [based on Balter et al. (42)] (percentage of all past-year users)

Country	3 mo or less	12 mo or more
Belgium	46.7	33.2
Denmark	59.8	10.9
France	58.0	31.5
Germany	75.4	14.1
Great Britain	61.5	27.4
Italy	79.3	14.2
Netherlands	67.6	22.5
Spain	61.9	26.5
Sweden	91.5	6.2
Switzerland	80.9	8.4
United States	71.7	14.2

A number of reports of the 1979 survey have provided information bearing on patterns of use of anxiolytics (of which 84% was benzodiazepine use) and hypnotics. Unfortunately, the data on these patterns as determined in 1979 cannot be compared exactly with those found in the earlier survey, because at least in the published reports the cut-off points used to differentiate the patterns were not the same for the two surveys. However, the 1979 data indicated (756) that 62% of those who reported having used an anxiolytic medication in the year prior to interview were short-term users; i.e., their longest period of regular daily use was 13 days or less, although about one in four of this group had used anxiolytics on a total of 30 days or more during the previous year. Another 18% reported regular daily use for at least 2 wk but less than 3 mo. The remaining 20% reported daily use for 4 mo or more; most of this group, or 15% of all users (1.6% of the total population), had used anxiolytics daily for 12 mo or longer.

The characterizations of short- and long-term anxiolytic users in reports of this survey were particularly interesting. According to one report (756), short-term users were much more likely than others to report having experienced side effects of these medications (mainly drowsiness), had more negative attitudes toward the use of tranquilizers in general, and were more likely to report moderate to heavy consumption of alcohol. Although they were less likely to have had chronic or severe medical or psychiatric problems, they were more likely to report that, as a result of psychological problems, they had experienced relatively prolonged role impairment in the previous year; role impairment was defined in terms of ability to keep up with one's responsibilities in eight areas, e.g., as a parent, as a spouse, at work, etc. The authors of this report offered some interesting speculation about this finding (p. 33):

> It may be ... that their negative attitudes toward psychotherapeutic drugs are part of a broader anti-psychological bias that leads them to under-report emotional symptoms. Their relatively heavy use of alcohol may, in addition, help to account for the elevation in role impairment.

Another report (755) focused on the long-term users, and specifically on those who reported having used these drugs regularly for a year or longer. This group was comprised of the 3% of all anxiolytic users who had used them regularly for 1 to 3 yr, 6% who had used them regularly for 3 to 7 yr, and another 6% who had used them regularly for 7 yr or longer. These long-term users tended to be older than other users; 71% were 50 or older (as opposed to 48% of other users), and a third of them were at least 65. The factor that most clearly distinguished these long-term users from others was that they

were much more likely to have multiple health problems (a difference that remained after statistically controlling for age); 75% of them, as opposed to 60% of other users and 28% of nonusers, reported that they had had multiple somatic health problems in the prior year. They were also more likely than others to have sought help from mental health professionals in the prior year, although most appeared to rely on help from primary care physicians. Of these long-term users, 69% reported that they had discussed their use of anxiolytics with their physician within 4 mo of their last use of their medication. This finding suggests that physicians generally do maintain some surveillance of patients receiving anxiolytic medications for long periods of regular use. The investigators noted that, as they had discovered in earlier studies, anxiolytic therapy is (p. 379):

> at least as likely to be directed to patients with a primary diagnosis of a physical disorder as to those with a primary diagnosis of a mental disorder. . . . We have now found that the major physical health problem of the long-term user was likely to be chronic—a finding that may help to explain, even if it does not necessarily justify, the long-term duration of use of anxiolytic medications.

An analysis (757) of the use of prescribed hypnotics, based on the 1979 NIMH survey, found that, for 74% of those who reported having used sleeping medications during the previous year, the longest period of nightly use during the year was less than 2 wk; 54% had never used them for more than one or two nights at a time during the year. Most users (64%) reported that they had used hypnotics for a total of fewer than 30 days during the year. However, 11% of users reported that they had regularly used hypnotics for 12 mo or longer. Although respondents were apparently questioned about their use of specific hypnotic products, data relevant to individual agents or types of hypnotics were not reported.

c. REGIONAL AND MEDICAL PRACTICE DATA ON PATTERNS OF USE. **i. United States.** One regional U.S. study providing important information on patterns of consumption of psychoactive drugs was that reported by Hulka et al. (500, 501), as previously discussed in the introduction to this subsection (page 344). The basic objective of this study was "to document the extent of concordance and discordance between medications prescribed and medications consumed. . . ." In order to pursue this objective, the study had an unusual design, entailing collection of data from physicians regarding their drug prescriptions as well as household interviews with patients who received these prescriptions. All general practitioners and internists in Fort Wayne, IN, and adjoining townships were represented by means of a random sampling procedure; the patients studied were all those patients with congestive heart failure or diabetes mellitus who consulted the participating physicians during a 4-mo period. A total of 46 physicians and 357 patients participated. The study measures and results pertaining to psychoactive medications were described previously (page 344). To summarize these results briefly, of all categories of medications prescribed, only that of drugs acting on the CNS (chiefly tranquilizers) was associated with significantly greater than average scores for all four types of disconcordance measured. Patients were more likely to know the prescribed regimen but not to comply with it for this category than for any other category of medications; the nature of this noncompliance was that patients frequently took less of these medications than had been prescribed.

Similar findings have been reported by a number of other investigators who studied patterns of drug consumption in regions of the U.S. and other countries. Apsler and Rothman reported (23) an analysis of data bearing on patterns of use of tranquilizers and sedatives (not otherwise defined in the report) from a 1976 survey consisting of interviews with a systematic, random sample of 1,087 adults in the Boston Standard Metropolitan Statistical Area. Prevalence of use of these medications was consistent with that found in national-sample surveys. Of the 17% of respondents who had used tranquilizers in the 8 mo prior to interview, 39% reported taking less than prescribed, 57% took exactly as much as prescribed, and 3% took more of these medications than prescribed. Of the 7% of respondents who had taken sedatives in the prior 8 mo, 20% took less than prescribed, 73% took exactly as much as prescribed, and 7% took more than prescribed.

A survey of patients of a family practice clinic, reported by Bush et al. (146), was limited with respect to representativeness because it proved impractical to employ a random procedure for selection of respondents and because the investigators experienced considerable difficulty in recruiting participants, so that the study sample may have been biased; however, these limitations for studies of this kind may be inherent in the clinical setting, and the data provided are relevant and interesting. Survey respondents were among those patients who had first received sedative-hypnotic prescriptions from the clinic within 2 yr prior to the study, which was conducted in 1979; 190 such patients were interviewed. Of the sedative-hypnotics that had been prescribed for these patients, 60% were benzodiazepines. The study found that prescriptions called for daily dosages within the recommended therapeutic range, with two possible exceptions (both prescriptions for barbiturates). Nearly half of the diagnoses for which these prescriptions were issued were of physical rather than mental problems, although the patients identified the reasons for drug use as psychological in 70% of responses. Seventy-three % of the patients reported that they occasionally (49%) or always (24%) took less of their medications than prescribed. Thirteen % of the patients were classified as possible "misusers" of their most recent sedative or hypnotic; 10% admitted to sharing the medication with

others, and 4% reported taking the drug more often than prescribed, though for a brief period of time.

Caplan et al. (153, 154) surveyed 675 people in the Detroit area, of whom more than half were selected on the basis that they had recently filled a prescription for diazepam; the other respondents constituted a control group, excluding persons who had recently filled a prescription for a psychoactive medication. Respondents were interviewed 4 times, at intervals of 6 wk, in 1981. With respect to demographics and health status, diazepam users in this survey were similar to anxiolytic users in national samples. As in the study reported by Bush et al. (146), prescriptions called for daily doses within the recommended range; fewer than 9% of prescriptions called for daily doses of 30 mg or more. During periods of drug use, most patients took a single daily dose. Of the diazepam users whose prescriptions had indicated specific regimens (rather than "as needed"), about 40% reported taking the medication exactly as prescribed, 3% took more than prescribed, and 58% took less than the prescribed dose. About one third reported using diazepam "only once in a while," while almost half reported daily or almost daily use in periods when they were taking the drug. This proportion of daily or almost-daily users is higher than that reported in surveys of yearly prevalence of use of anxiolytics (e.g., ref. 756), probably because the study design required that the subjects using diazepam had filled a prescription for the drug within the prior 6 wk, thus increasing the likelihood of selecting frequent users. Daily users of diazepam were significantly less likely to consume alcohol than nonusers; in addition, all users drank less alcohol during periods when they were taking diazepam than when they were not. The study found no evidence of recreational use or abuse of diazepam.

ii. United Kingdom. The Institute for Social Studies in Medical Care (London) conducted community surveys in 1969 and 1977 studying a wide range of parameters of medication use. The 1969 survey (262, 261) consisted of interviews with a sample of 1,412 adults representing 15 parliamentary constituencies in England, Wales, and Scotland. Ten % of the population (6% of men and 13% of women) reported that they had taken some prescribed sedative (i.e., sedatives, tranquilizers, or hypnotics) in the 2 wk prior to the interview; sedatives accounted for two-fifths of the prescribed medicines taken in this period. The most frequent reason given for this use was insomnia, which was reported more often by women (20%) than men (12%). Symptoms such as "nerves," "depression," or "irritability," which were also reported more often by women (27%) than men (14%), were given as the reason for sedative use by 30% of users. The proportion of people reporting insomnia and the proportion who were taking sedatives increased with age; however, the proportion of people reporting "nerves," etc. tended to decrease with age.

One of the most interesting aspects of this study (262, 261) was its focus on the duration of sedative use and on use of repeat prescriptions for the same drugs. Half of all prescribed drugs that adults had taken in the previous 2 wk had first been prescribed for them at least 1 yr earlier, and 63% were repeat prescriptions. Eight % of all respondents were taking sedatives that had first been prescribed more than a year earlier; these people comprised 32% of all patients who were users of long-term repeat prescriptions.

A similar survey, conducted in 1977 (17), consisted of interviews with a sample of 836 adults representing 20 parliamentary constituencies in England and Wales. This survey focused on the use of medications obtained through repeat prescriptions. The overall frequency of such prescribing was found to be similar in 1977 to that found in the 1969 survey (262, 261). However, whereas in 1969 about a quarter of peoples' most recent repeat prescriptions were obtained without seeing the physician, this proportion had risen to more than half (54%) in 1977; among users of psychotropics, this proportion in 1977 was nearly three fifths. The category of "psychotropics" as used in this report included sedatives, hypnotics, and tranquilizers (as in the 1969 survey), but also included antidepressants, stimulants, and appetite suppressants. This later report indicated that, of all patients who reported use during the previous 2 wk of a drug that had first been prescribed more than a year previously, 32% were taking psychotropics. However, the proportion of the total population taking psychotropics on a long-term basis had not increased between 1969 and 1977. Long-term use of all drugs in 1977 was found to increase with age, and 14% of all respondents aged 55 and over were taking psychotropics on a long-term basis (as compared with 3% of respondents between 18 and 34).

iii. Sweden. A series of studies conducted in the county of Jämtland by Boethius and Westerholm (98–100), although not interview surveys, provides information relevant to patterns of use of psychotherapeutic medications. These studies, which were described in detail in section V C 2 c above (page 333), examined purchases of hypnotics, sedatives, or minor tranquilizers by individuals over 5-yr periods. In brief, the studies found that, for groups of individuals with frequent or infrequent purchases of these drugs in the course of 1 yr, subsequent purchases of the same medications significantly decreased over 4 succeeding yr. However, some individuals increased the frequency of such purchases, and a few cases appeared to reflect overuse or abuse.

iv. New Zealand. Khan et al. (576) examined a sample of the case records of seven general practitioners in Christchurch city and suburbs and identified 87 patients who were currently using benzodiazepines. Of these patients, 69% were over 50, and 64% had chronic physical illnesses. The investigators compared the doses of benzodiazepines specified in the first and last recorded prescriptions for these patients; the results, shown in table 22, indicated a statistically significant positive association between duration of use and the likelihood of increases in daily doses. Of the 87 current users, 72 (83%)

TABLE 22

Change in prescribed daily dose between first and most recent prescriptions in relation to duration of use [based on Khan et al., 1981 (576, table 1)]

	Nos. of patients with the following duration of use				
	<2 yr	<4 yr	<6 yr	>6 yr	Total
No change or decrease	22	14	12	5	53
Increase	12	6	4	12	34
Total	34	20	16	17	87

had been using benzodiazepines regularly for longer than 6 mo. The investigators interviewed 40 of these long-term users who had not been using any other psychoactive drugs concurrently; 7 of these patients (17%) (p. 20):

> voluntarily reported that they were "dependent," "hooked," or "addicted." This conviction had set in following either accidental or intentional abrupt withdrawal when symptoms consisting of extreme anxiety, depression, depersonalization, sleep disturbances, and, in one case, features of acute organic brain syndrome had necessitated the restarting of the benzodiazepines.

5. Summary and discussion. With respect to the survey research reviewed above, the basic areas of interest relevant to assessment of the abuse liability of benzodiazepines are the extent of actual consumption of these medications; the appropriateness of this use; and the patterns of consumption, with particular emphasis on the extent and characteristics of long-term regular use. This section will summarize the chief research findings in each of these areas and will present a discussion of certain of the findings.

a. EXTENT OF USE. A cross-national survey to investigate adult use of certain psychoactive medications was conducted in nine Western European countries in 1971; comparable methods were used in another cross-national survey of these same nine countries, as well as Switzerland and the United States, in 1981. The 1971 study found that the 1-yr prevalence of use of anxiolytics was roughly comparable for the countries surveyed, ranging from 9.7 to 16.8% of the total populations, with an average prevalence of use of 14%. The 1981 study showed that the range of prevalence figures for the different populations had broadened slightly (7.4 to 17.6% of the populations) and that the extent of past-year use had declined in most of the countries surveyed, so that the average 1-yr prevalence of use of anxiolytics was 12.5% (or 12%, considering only the nine countries surveyed at both times).

Prescription sales data have indicated that use of anxiolytics in the U.S. increased to a peak in about 1975 and then began to decline; similar curves have apparently characterized rates of use in many or most other countries, though within varying time frames. Thus, it appears most accurate to view the prevalence figures for 1971 and 1981 as two points in a curvilinear pattern of change.

Both the 1971 and the 1981 surveys found a higher prevalence of anxiolytic use among women than among men of virtually every age category in all countries surveyed. In most countries, prevalence of anxiolytic use increased with age.

Surveys of nationally representative samples of U.S. adults, using methods comparable to those employed in the cross-national surveys summarized above, were conducted in 1970–1971 and in 1979. The 1-yr prevalence of use of anxiolytics found in the earlier study was 12%; in the 1979 study, it was 11%. These figures indicate that the rate of use of anxiolytics in the U.S. is approximately in the middle of the range of the Western European nations surveyed. According to the 1979 study, the past-year prevalence of use specifically of benzodiazepine anxiolytics among U.S. adults was 9%.

These U.S. surveys also found that physicians tend to be conservative in prescribing anxiolytics and that the public generally holds negative attitudes toward the use of tranquilizers, which are manifest in conservative patterns of consumption. Comparison of the data from the two surveys indicated that this conservatism, on the part of both physicians and the public, had increased between 1970–1971 and 1979.

In 1979, 4.3% of the U.S. adult population reported having used some prescription medication within the past year to promote sleep. Use of a drug specifically indicated as a hypnotic was reported by 2.4%; this represented a decline from 3.5% in 1970–1971.

b. APPROPRIATENESS OF USE. Probably the best available evidence pertaining to the appropriateness of actual use of benzodiazepines comes from surveys in which samples of the general population are interviewed about their drug use and are rated on scales indicating psychological status.

A 1970–1971 survey of a nationally representative sample of adults in the U.S. found that about 27% of the population (19% of males and 34% of females) reported high levels of psychic distress during the year prior to interview. Of these respondents, 30% had used a prescribed anxiolytic during the prior year, while 8% of those with low ratings of distress had used such medications. Analysis of data from a comparable survey, conducted in 1979, attempted to correlate respondents' self-ratings with DSM-III diagnostic criteria; this analysis determined that about 10% of the sample had experienced symptoms corresponding to recognized syndromes of clinical anxiety. This proportion of the population was lower than that reporting high psychic distress in the earlier survey and lower than might be expected based on clinical experience or on other epidemiological research (910). However, the findings were similar to those of the earlier survey with respect to the proportion of the distressed population that had used anxiolytic medications; of those with symptoms corresponding to the DSM-III generalized anxiety disorder, 27% had used anxiolytics during the previous year.

Data bearing on appropriateness of anxiolytic use from regional and medical practice surveys conducted in the U.S. and other countries tend to confirm the general appropriateness of the actual use of anxiolytics. These studies indicate that users of these drugs have high levels of emotional distress, as measured on a variety of standard self-report instruments. They also provide evidence that patients given prescriptions for benzodiazepine anxiolytics tend to take less than the doses prescribed and tend to reduce their use over time. Where these studies have sought evidence of misuse of these agents (e.g., recreational use, increasing doses, nonmedical use), either by formally incorporating relevant measures in the study design or by secondary analysis of study data, they have found little or no misuse.

Some studies have found that benzodiazepine tranquilizers are widely prescribed and used in patients whose primary psychological problems are conditions other than anxiety (e.g., phobias, panic disorder, depression), for which other psychoactive classes are generally regarded as the agents of choice. In some cases, the benzodiazepines have been used together with these more specific agents, presumably for accompanying anxiety; in other cases, the benzodiazepines alone have been used. In general, these patterns of drug use reflect on the primary care settings to which most patients bring most psychological problems and raise questions about the ability of primary care physicians to arrive at appropriate differential diagnoses of these problems and to select appropriate pharmacological and other treatments for them.

The challenge to primary care physicians was clearly summarized by Goldberg and Bridges (367), who studied 380 patients with emotional problems that they were presenting for the first time to general practitioners in the Manchester (United Kingdom) area. Of the 59 patients with generalized anxiety disorder, 27% presented symptoms of an accompanying physical illness and did not mention any anxiety symptoms unless the physician asked about these explicitly; a further 60% presented somatic manifestations of anxiety; and only 13% specifically presented psychological symptoms.

These findings shed some light on the survey data, reviewed in this section, indicating that most people with psychological problems do not receive pharmacological or other treatments for these problems. Apparently only a relatively small proportion of emotionally troubled people seeks medical care for these problems; of those who do, most consult primary care physicians, to whom they do not report their problems in terms of psychological distress. Thus, a considerable burden is placed on the primary care physician, who has furthermore not received extensive formal training in diagnosis or treatment of psychological problems. It bears repeating, then, that a primary lesson emerging from the epidemiology of benzodiazepine use is the need for systematic investigation of emotional disorder as it is presented, diagnosed, and treated in primary care settings; such research could be the basis for substantially improving the care available for these problems, in part by increasing the probability that patients will get appropriate prescriptions for either benzodiazepines or other psychoactive agents where these might be more specifically beneficial.

c. PATTERNS OF USE. In all countries that have been surveyed, with the exception of Belgium, most people who use anxiolytics use them only occasionally or for relatively short periods of consecutive daily use, i.e., for less than a month at a time. However, a significant proportion of those who use these medications have used them for longer periods. In 1981, an average of 19% of all past-year users in 10 Western European countries and the United States reported that they had used anxiolytics daily for 12 mo or more; this included between 0.5 and 5.8% of the total adult populations of these countries.

National data for the U.S. provide a closer look at these patterns of use, and particularly at the correlates and characteristics of long-term use. In 1979, 15% of U.S. users reported having used prescribed anxiolytics for 12 mo or longer; this included 3% whose daily use had lasted from 1 to 3 yr, 6% from 3 to 7 yr, and another 6% for 7 yr or longer.

In the same U.S. national-sample survey, conducted in 1979, 11% of those who had used prescribed hypnotics in the previous year also reported daily use for 12 mo or longer.

Of those who had used anxiolytics daily for a year or longer, 71% were 50 or older, as opposed to 48% of other users. These long-term users were most clearly distinguished from others, however, in that they were much more likely to have multiple somatic health problems—illnesses which tended to be chronic. Accordingly, they were also more likely to have visited physicians frequently in the previous year, and 69% reported that they had discussed their anxiolytic use with their physician within 4 mo of their last use of this medication; this suggests that physicians generally do maintain frequent surveillance of patients receiving chronic anxiolytic treatment.

These data provide a portrait of the chronic user of anxiolytics, and thus indirectly of the anxious individual, that contrasts dramatically with popular stereotypes. The chronic user of these medications is typically an elderly person, probably a woman, afflicted by multiple chronic physical ailments, with related or unrelated emotional problems, for whom these health problems and their medical care comprise a central feature of daily life.

d. LONG-TERM USE. The absolute prevalence of long-term use of anxiolytics and sedatives seems strikingly high. While most users use benzodiazepines for short periods, most use (in terms of the percentage of these drugs actually consumed) is by the 15 or 20% of users who use these drugs regularly for virtually indefinite periods. These findings have understandably provoked

considerable discussion, centering around a few basic questions. Is the proportion of long-term users increasing? How does the pattern of long-term use develop? Why do some patients continue to use psychotropic drugs for years? Does long-term use of benzodiazepines reflect dependence or abuse?

i. Is the proportion of long-term users increasing? Marks (713) and Williams (1150) have suggested that the proportion of psychotropic users who use these drugs for long periods has increased substantially, at least in the United Kingdom. As indicated by the evidence they cite, there may have been an increase in the proportion of repeat prescriptions for psychotropics and, especially, in the proportion of such repeat prescriptions that patients obtain without consulting their physicians (17). However, Williams (1150) based his suggestion regarding an increase in prevalence of long-term psychotropic use chiefly on the report by Marks (713), and it is not clear that the studies upon which Marks (713) based his conclusion are methodologically comparable.

Woodcock (1169) examined the records of 20 general practitioners in London and the Home Counties to identify all patients who had been receiving regular psychotropic prescriptions for a year or longer as of a certain day in 1967 and as of the same date in 1957; psychotropics included hypnotics, tranquilizers, and stimulants/appetite suppressants. Comparison of data for those 2,274 patients for whom records were available for both of these dates indicated such long-term use for 31 patients (1.4%) in 1957 and 89 (3.9%) in 1967; considering only patients who were 20 or older (i.e., those most likely to be prescribed psychotropics), the figures would be 2.0% in 1957 and 4.1% in 1967. As Woodcock noted, since these patients were obviously 10 yr older in 1967, and since long-term use was found to increase with age, one would have expected some increase in the proportion of long-term use among these patients as a function of age alone; however, the increase observed was considerably greater than that expected as a result of age alone, which the investigator interpreted as evidence that the proportion of long-term users had actually increased in this 10-yr period.

However, Parish (848), who also studied the records of a large group of United Kingdom general practitioners (in a Midland industrial city) for 1967–1968, found that 1.9% of the adult (15 yr or older) patient population had received psychotropic prescriptions sufficient to provide regular doses for a year or longer; psychotropics in this study included the same types of drugs included by Woodcock, as well as antidepressants. If this figure for 1967 were compared with the 1957 figure reported by Woodcock (1169), it would indicate no change in the prevalence of long-term use.

Household surveys of medication use conducted by Dunnell and Cartwright in 1969 (262) and by Anderson in 1977 (17), both from the Institute for Social Studies in Medical Care, used comparable methods (797). Both studies found that 7% of the adult population of the United Kingdom were using psychotropic medications that had first been prescribed for them at least 1 yr earlier; psychotropics included the same types of drugs included in the study by Parish, as described above. This rate of long-term use is much higher than those found in the other studies described above, presumably because patients were classified as long-term users even if they had received only two prescriptions for the same drug, so long as these prescriptions were written with an interval of at least 1 yr; i.e., these rates did not necessarily refer to the duration of continuous or regular use.

This raises an important point with respect to the interpretation of these data in general (and with respect to the extent to which data on "long-term use" can be applied to the issue of dependence liability in general; see discussion on page 364 below). The point is that, partly because of differences in survey techniques and partly because of inherent ambiguities in the meaning of "regular" use, it is quite uncertain that most estimates of the prevalence of long-term psychotropic use really apply to continuous drug use. In this light, and in view of the studies reviewed above, it seems by no means clear that the overall prevalence of psychotropic use has increased, at least among adults in the United Kingdom.

ii. How does the pattern of long-term use develop? Some early information on this question was provided in the study by Woodcock (1169), as discussed above. This study sampled medical records to identify patients who were long-term users of various psychotropic drugs in 1967 and in 1957. At both of these dates, long-term regular use of psychotropics increased with age, and most long-term users in all age groups were women. Woodcock examined the histories of the 31 patients who had been long-term users in 1957 and commented (p. 160):

> . . . Once embarked on a daily intake of a psychotropic drug for any length of time, the patient is not easily weaned from it. Fewer than one-quarter of these 31 patients had ceased continuous medication by 1967. Of the 24 who were still [regular users] in 1967, only 6 had had any interruption of [regular use] during the intervening 10 years.

Most of the information available about long-term use of anxiolytics and hypnotics is derived from retrospective studies of medical practice records and from cross-sectional interview surveys in which people are asked about their use of medications. These types of research are inherently limited with respect to the amount of information they can provide about many of the questions surrounding long-term use. The question of how long-term use develops, as well as other centrally relevant questions about long-term use, will ideally be addressed by prospective longitudinal studies in which patients are followed from the time that they receive psychotropic prescriptions—preferably, from the time that they re-

ceive such prescriptions for the first time, although this criterion might make such a study quite impractical. Such studies are in fact extremely difficult in practical terms, and it is not surprising that only a few have been reported; these do, however, provide some very interesting evidence about long-term use, which helps to fill in the picture outlined by other data sources.

Clift (180–182) prospectively studied patients of a group general practice in Manchester (United Kingdom) who presented with insomnia of recent origin. One group, of 50 patients, was given prescriptions for nonbarbiturate hypnotics, chiefly nitrazepam; the patients were told they could obtain repeat prescriptions if they needed them. At 1 yr following the initial prescriptions, 16 patients (32%) were continuing to receive repeat prescriptions for regular use of these hypnotics; this percentage subsequently declined only very gradually, so that about 15 or 20% of the group (after adjustments for followup attrition) was still using these drugs regularly 4 yr after the initial prescription. A second group, of 102 similar patients, was given prescriptions for either amobarbital (100 mg) or nitrazepam (5 mg), according to a randomization procedure; these patients also were told they could have repeat prescriptions if necessary, but with the admonition that they should try to manage without hypnotics as soon as possible. One yr following the initial prescriptions, eight patients (8%) were still receiving repeat prescriptions; five of these were taking nitrazepam and three were taking amobarbital. At 2 yr after the initial prescription, 8% of the patients were continuing to take these drugs on a regular basis, but the investigator noted that, including patients who were using the hypnotics on an intermittent or episodic basis, altogether 15% of the original group (after adjustments for attrition) were taking these drugs at the 2-yr followup. A number of parameters regarding patients' histories, diagnoses, and scores on various psychological tests were examined in the interest of identifying determinants of recurrent and/or continuous use. This analysis indicated that patients who had discontinued use of hypnotics were most likely to resume use at times when they were experiencing temporary increases in "personal disturbance" and that the patients who became long-term regular hypnotic users were more likely to have received hypnotics at previous times and to have psychiatric problems underlying their insomnia.

Although the numbers of patients in these studies were rather small, as one might expect in research of this kind, the difference between the groups with respect to prevalence of long-term use (32% versus 8% at the 1-yr followup) seems worth remarking. Clift (180) attributed this difference to the admonition given to the second group that they should try to manage without the drugs as soon as possible. There was no evidence that dependence had developed in these patients; however, if physiological or psychological dependence did develop, it was apparently not of sufficient severity to override the physician's admonition.

Further information about the development of long-term use patterns comes from a pilot study reported by Williams et al. (1151) and by Murray et al. (798). This was a prospective, longitudinal study of 153 patients who received a prescription for a minor tranquilizer, hypnotic, or antidepressant for the first time (or at least for the first time in at least 3 mo). Of 124 patients who could be followed up, 26 (19%) continued to receive these drugs for at least 6 mo. The investigators noted that chronic physical problems were frequent among these long-term users, but statistical tests failed to show that these were significantly associated with long-term use. The factors most strongly predictive of long-term use were age over 45, previous use of psychotropic medications, and severity of psychiatric illness. The investigators also noted that psychiatric illnesses among the long-term users tended to be recurrent problems of long duration. They also found that many patients attributed the onset of their current symptoms to a life crisis and noted that, in the cases of those who developed long-term use patterns, these symptoms might have persisted for long periods because they tended to have less social support than other patients; in this connection, they cited Balint et al. (36), who had also found that patients receiving repeat psychotropic prescriptions for long periods were often characterized by social isolation. On the other hand, Clift (180) had found no difference between patients who became long-term hypnotic users and those who did not with respect at least to the proportions who were widowed or divorced.

In sum, studies in which psychotropic users have been followed over time tend to support some of the determinants of long-term use suggested by other research, such as advanced age and psychiatric impairment. Perhaps the most important contribution these studies have made to date to our understanding of these determinants is that long-term use is most likely to develop in patients with recurrent psychiatric problems of long duration, for which they have previously received psychotropic medication.

iii. Why do some patients continue to use benzodiazepines for years? There is some evidence that long-term use of benzodiazepine anxiolytics remains effective, as measured by standard psychiatric rating scales (125, 919), and that most patients who have discontinued anxiolytic treatment relapse within a year, suggesting that they might have benefited from continued "maintenance" therapy (918). However, cross-sectional community surveys consistently demonstrate that most people using anxiolytic medications are indeed anxious; while this evidence speaks favorably to the appropriateness of use of these drugs, the other side of this coin is that these people are anxious despite the fact that they are using these drugs.

This apparent paradox of cross-sectional survey research has been addressed in a prospective longitudinal study of diazepam use, as reported by Caplan et al. (154). This study measured a wide array of social and psychological variables in the lives of the subjects, including a group of people who had recently filled a prescription for diazepam and a control group of nonusers. Like the cross-sectional surveys, this study found a positive association between diazepam use and anxiety when measured at any single point in time. However, the investigators were able to explore this association in a broader context, i.e., the interaction of each of these variables with other factors in the subjects' lives, over time. This enabled them to address the causal significance of the association: does anxiety lead to benzodiazepine use? Does benzodiazepine use lead to anxiety? When they applied statistical analyses to control for other factors in the subjects' lives, the investigators found that the positive association between anxiety and diazepam use virtually disappeared. That is, these phenomena were not related to each other in a causal manner; rather, each was determined by relatively stable antecedent variables—specifically, the higher initial levels of anxiety, more stresses, and poorer health of the diazepam users as opposed to the control group of nonusers.

This perspective agrees very well with the findings reviewed here regarding the determinants of long-term use of anxiolytics. This pattern is most likely to develop in older people, who probably have multiple chronic physical problems and associated emotional problems (755); who have recurrent psychiatric problems of long duration (798, 919), possibly sustained or exacerbated by inadequate social support (35, 798, 452); and who, when they have sought help, have recurrently received prescriptions for psychotropic drugs—often benzodiazepines—of which they have gradually become regular long-term users (921, 1151).

The question, however, remains why these people continue to use these drugs for such long periods. As mentioned above, there is some evidence for the long-term efficacy of the benzodiazepines, as measured by standard psychiatric ratings—but not much. There are, however, suggestions that at least some patients might continue to experience subjective benefits from use of these drugs over long periods. Hollister et al. (485) studied 108 neurosurgical patients who received diazepam regularly for long-term (median, 5 yr) management of muscle spasm, pain, and associated anxiety and insomnia; he found no evidence of increased tolerance, and 83% of the patients considered the medication still beneficial. In the prospective study of psychotropic use reported by Murray et al. (798), 15 of the 19 long-term users regarded the drugs as helpful, and "most expressed a desire to give up the drugs, but were deterred by the fear of their symptoms returning."

Similar findings were reported by Lucki et al. (681), who studied 43 patients who had been taking benzodiazepines for at least 11 mo (average duration of use was 5 yr) and a control group of 26 anxious patients who had not been chronic users of benzodiazepines and had been drug free for at least 3 wk prior to study. Seventy-five % of the chronic benzodiazepine users reported that continued use of these medications helped to control their anxiety symptoms, and ratings of "tranquilization" on a standard scale for assessment of mood states were significantly greater for the benzodiazepine group than for the untreated anxious control group.

Helman (452) conducted in-depth interviews with 50 patients selected at random from among all patients who consulted National Health Service (United Kingdom) general practitioners during a 6-mo period in 1979 and who had been receiving repeat prescriptions for benzodiazepine anxiolytics or hypnotics for at least 6 mo. With regard to perceived effects of drug ingestion, 13 (26%) said the drug made them fall asleep (it is not stated whether this was the intended effect); 17 (34%) noted some improvement in their mental state; and 20 (40%) noticed no subjective change. Thirteen of these 20 patients speculated that the drug's effect was "probably psychological," i.e., as opposed to a pharmacological effect. The patients were asked what they would have done if their medication were discontinued or not available; the results are shown in table 23.

In the absence of substantial evidence that long-term use of benzodiazepines is effective, some investigators (e.g., refs. 838 and 867) have made the assumption that the explanation for chronic use of benzodiazepines must pertain to their potential for producing dependence, and they have urged physicians to gradually discontinue these medications in their patients who have used them for long periods. It is not clear, however, that this assumption can be supported. Previous sections of this review (as well as some of the studies reviewed in this section, e.g. ref. 798) have concluded that patients using benzodiazepines would prefer not to take them if they felt they could manage without them; and that, while physiological dependence can occur over long periods of regular use, withdrawal from therapeutic doses can generally be managed with little difficulty or discomfort. Since the data reviewed in this section (e.g., ref. 755) indicate that long-term users are likely to be in frequent contact with their

TABLE 23

Patients' strategies if drug were withdrawn or unobtainable [from Helman, 1981 (452, table 4)]

	No.	%
Taken another drug	18	36
Done without and coped well	14	28
Don't know	8	16
Continued with symptoms as before	5	10
Suffered a "breakdown"	3	6
Seen a psychologist	1	2
Gone on a "nature cure"	1	2

physicians, it would appear that they have sufficient opportunity to discontinue anxiolytic treatment in an appropriate manner, if they or their physicians wish to do so. Apparently many do not.

Why not? The possibility must be considered that there is a population subgroup that is peculiarly susceptible to some effect of benzodiazepine use that does not appear in broad samples of the anxious population, and that this effect might be responsible for long-term regular use among this subgroup. Some hypotheses that might be considered in this connection are as follows. (*a*) Benzodiazepines might serve as reinforcers in a certain subgroup of the anxious population. (*b*) Benzodiazepines might produce physiological dependence associated with unusually difficult or uncomfortable withdrawal in a certain subgroup. (*c*) Long-term use of benzodiazepines might remain effective in reducing psychiatric morbidity in a certain subgroup, in a manner which may not be measurable using current available psychiatric rating techniques. (*d*) Benzodiazepines might produce some other long-term benefit in a certain subgroup, which may or may not be measurable using current available rating instruments; this may have to do, for example, with maintaining certain types of social functioning.

Another general kind of explanation for chronic anxiolytic use is suggested by survey research (828), not reviewed here, indicating that older people tend to have more fatalistic attitudes than younger people about their health, that they tend to feel their health does not depend so much on what they do themselves, that they have more confidence than younger people in health care institutions in general and specifically in their personal physicians, and that they are more likely than younger people to comply with their doctors' prescriptions for medications. If they also have multiple chronic physical disorders, as the present findings indicate about long-term anxiolytic users, they are likely to be using numerous drugs regularly and chronically. It is conceivable, then, that these are individuals who have perhaps unavoidably fallen into a pattern of medication-taking, in which they cannot discriminate the effects of the various drugs prescribed for them, so that, unless a particular medication produces some distinct adverse effect, they continue taking all the drugs prescribed for them regardless of clinical effectiveness or even of subjective effect. This possible explanation for patients' continued use would not, however, account for physicians' continued prescriptions for such patients. On the basis of the available epidemiological evidence, it does not seem likely that many physicians would continue to prescribe anxiolytics for long periods in the absence of some rationale for doing so. This consideration, then, argues for the hypothesis that long-term users associate this medication with some perceived clinical, social, and/or subjective benefit, which motivates them and their physicians to continue its use.

iv. Does long-term use of benzodiazepines reflect misuse or dependence? Although it seems clear that tolerance can be demonstrated readily to the benzodiazepines' effects on psychomotor performances, there are discrepant findings with respect to the incidence of tolerance to the drugs' sedative or anxiolytic effects. Some studies (e.g., refs. 698, 465, and 445) have indicated the development of such tolerance, while others (485, 681) have found no evidence of tolerance to the anxiolytic effects of benzodiazepines over long courses of treatment. As discussed above in section III C (pages 279 to 285), there are also discrepant findings regarding the development of dependence to chronic administration of therapeutic doses of benzodiazepines.

It seems very likely that all patients are in fact susceptible to dependence to therapeutic doses of benzodiazepines, given chronically for sufficiently long periods. However, while many patients identified as "long-term users" may be using benzodiazepines over long periods of time, they may not be using them continuously over these periods. For example, serial measurements of plasma levels of benzodiazepines and their active metabolites have revealed substantial intraindividual variations among patients presumed to be using the same dose regularly (485, 919). In addition, a number of clinical investigators (e.g., refs. 485, 125, and 921) have commented on the difficulty of finding "long-term benzodiazepine users" who were actually using these drugs on a continuous basis; interviews with over 200 patients who were represented by their physicians and by themselves as long-term benzodiazepine users indicated that "half of these patients used benzodiazepines only as needed . . ., certainly not when on vacation, and frequently not every day nor on weekends" (921). Thus, it may be, as Rickels and coworkers speculated based on this experience, that the prevalence of long-term regular use is substantially overestimated in community surveys.

Nevertheless, some proportion of long-term users must use benzodiazepines continuously. Does this long-term use constitute misuse? If future research determines that there is a subgroup of the anxious population in whom the benzodiazepines serve as reinforcers or produce physiological dependence associated with unusually severe withdrawal and that this dependence is primarily responsible for a substantial proportion of the long-term use of these drugs, then this long-term use would appear to reflect inappropriate use of these drugs, in that these patients might be exposed to the risks of the medications in the absence of equivalent or greater benefit. For the present, however, the available evidence reveals no particular risk associated with long-term use of benzodiazepines, other than the risk of physiological dependence itself, whereas the patients using these drugs for long periods and their physicians apparently recognize some benefit which they find sufficiently compelling to justify this chronic use. There is a great deal about the circum-

stances of these users—who are most likely to be older patients with recurrent emotional disturbances and multiple chronic somatic ailments—which has not been elucidated by research to date. While many of these patients may indeed be physiologically dependent on benzodiazepines, the harm represented by this condition in itself does not seem sufficiently compelling to justify imposing on these patients and their physicians the judgment that they are abusing these medications.

F. Use in Special Populations

1. Elderly patients. a. PREVALENCE OF USE. **i. Noninstitutionalized elderly.** As described previously (section V E 1 b), in 1981 Balter et al. (42) conducted a cross-national interview survey regarding the use of antianxiety and sedative agents (excluding hypnotics). Based on the findings of this survey, table 24 presents data on the elderly populations (65 yr or older) of nine Western European countries and the U.S. who reported having used a medication of this type in the year prior to interview. The column designated [A] indicates the percentage of the population of each country that reported use of antianxiety/sedative agents in the year prior to interview; column [B] indicates the proportion of elderly users in each country as a percentage of the entire elderly population of that country. Thus, comparison of columns [A] and [B] indicates that an average of 12.5% of these total national populations, as opposed to 15.4% of the elderly populations of these countries, reported use of anxiolytic/sedative medications. Elderly users were particularly overrepresented in Sweden, the Netherlands, and Belgium; elderly users were not overrepresented, however, in Italy, Great Britain, or the U.S.

Although not displayed in table 24, data from this report (42) also indicate that women were overrepresented among elderly users of anxiolytics and sedatives in every country surveyed except France. Women represented 57% of all elderly users in Switzerland; 60% or more in Belgium, Italy, and Spain; and over 70% in Germany, Great Britain, the Netherlands, Sweden, and the U.S.

TABLE 24

Twelve-mo prevalence of use of antianxiety/sedative agents among age groups 65 or older in 1981 [data on prevalence of drug use based on Balter et al., 1984 (42)]

	[A] Population using antianxiety or sedative agents (%)	[B] Users 65 or older as % of population who were 65 or older
Belgium	17.6*	26.7
France	15.9	17.5
Germany	11.3	14.9
Great Britain	11.2	10.2
Italy	11.5	8.5
Netherlands	7.4	12.0
Spain	14.2	17.3
Sweden	8.6	16.1
Switzerland	14.6	18.5
U.S.A.	12.9	12.6

* Population statistics based on Demographic Yearbook, 1982, United Nations, New York, 1984, and Demographic Yearbook, 1984, United Nations, New York, 1986.

Mellinger and Balter (752) also conducted a national-sample survey of the use of various types of psychoactive drugs in the U.S. They found that the past-year prevalence of use of anxiolytics increased with age to a peak (16.3%) in the group aged 50 to 64 and declined to 15.3% among those aged between 65 and 79 (the highest age sampled). The rate of use among females was higher than that among males in all age groups; among the elderly, 18.7% of females and 9.1% of males reported use of an anxiolytic in the past year. Use of hypnotics increased linearly with age and reached 6.0% (5.3% for males and 6.5% for females) among those between 65 and 79.

These data are summarized in table 25, together with data from several other interview surveys conducted in the U.S., Canada, and Denmark. Considering the data shown for the U.S., which are listed by date of survey, it will be seen that the past-month prevalences found by Eve and Friedsam (279) appear considerably higher than would be expected from the past-year rates found by Mellinger and Balter (752); it should be noted that the data from the former study included both nonprescription and prescription drugs and that the population surveyed included people between 60 and 64 as well as older people. The data from the two Dunedin program studies (422, 423) represent drugs in "regular use," which may have been intended simply to mean drugs for which the respondents had prescriptions, regardless of their actual consumption patterns. The prevalence figures for use of diazepam, chlordiazepoxide, and flurazepam from the Canadian study (1) do pertain to current prescriptions for these drugs, regardless of actual consumption patterns. On the other hand, the prevalence figures reported in the study from Denmark (459) pertain to drugs that were used on a daily basis; these included both prescription and nonprescription sedatives and hypnotics, including barbiturates, chloral hydrate, and meprobamate, as well as benzodiazepines.

Information on the rates of prescription of anxiolytics, sedatives, and hypnotics for elderly versus younger patients is available from the NAMCS, a survey of a national sample of office-based physicians in the U.S. (described in more detail in section V D 1 a). Koch and Campbell reported (588) data from this survey, pertaining to the frequency of office visits in 1980 and 1981 which resulted in the prescription of antianxiety agents, sedatives, or hypnotics; benzodiazepines comprised 77% of this medication category. The relative frequency of prescriptions for these drugs increased with age up to the group aged 50 to 54, declined somewhat for those aged 55 to 59, increased to a second peak for those 65 to 69, and then steadily declined with advancing age. This

TABLE 25

Interview studies of prevalence of use by elderly in the general population

Study	Sample	Locality	Date of survey	Period in which drug was used	% using	Type of drug	Age group
Eve and Friedsam, 1981 (279)	Sample of persons 60 or older in a needs assessment survey, comprising 70% of older population of state	U.S.A.: TX	1974	Past mo	22 12	Tranquilizers Hypnotics	60+
Hale et al., 1985 (423)	Participants in a hypertension screening program (n = 1,711)	U.S.A.: Dunedin, FL	1977–78	Regular use	8.7 0.9 5.9	Tranquilizers Sedatives Hypnotics	65+
Stewart et al., 1982 (1041)	Participants in a hypertension screening program (n = 3,192)	U.S.A.: Dunedin, FL	1978–80	Regular use	5.7 2.2 0.5 0.3	Diazepam Chlordiazepoxide Clorazepate Oxazepam	65+
Mellinger and Balter, 1983 (752)	Sample of U.S. population (n = 3,161)	U.S.A.	1979	Past yr	15.3 6.0	Anxiolytics Hypnotics	65–79
Achong et al., 1978 (1)	Chronically ill patients referred to an assessment and placement service (n = 1,842)	Canada: Hamilton-Wentworth County, Ontario	1976	Current use	15.7 3.1 27.5	Diazepam Chlordiazepoxide Flurazepam	65+
Hendriksen et al., 1983 (459)	Random sample of elderly population of a municipality	Denmark: Rodovre Municipality	1980	Daily use	24	Sedatives and hypnotics	75+

overall pattern agrees with that found in the national interview survey described above (752).

NAMCS data for 1980 and 1981 also indicate that anxiolytics, sedatives, or hypnotics were prescribed at 4.0% of all office visits by patients under 75, at 5.7% of visits by those 75 to 79, 6.6% of visits by those 80 to 84, and 4.0% of visits by patients 85 or older (589).

Data from the NDTI (508), another survey of a national sample of office-based U.S. physicians (described in more detail in section V D 1 a), indicate that, in 1986, 26% of prescriptions for benzodiazepine minor tranquilizers and 40% of prescriptions for benzodiazepine hypnotics were issued to patients 65 yr of age or older. An analysis of NDTI data, together with retail sales data, found that use of benzodiazepines in the U.S. in 1984 increased with age, and that this was due chiefly to the prevalence of use of benzodiazepine hypnotics among the elderly (545).

National data bearing on relative rates of prescribing of these drugs for elderly versus other patients are also available for Australia. Chapman (164) compared the volume of prescriptions for various types of psychoactive drugs reimbursed in 1973 through 1975 under the General and under the Pensioner Prescription Pharmaceutical Benefits Schemes. He found that pensioners (of whom 87% were aged, i.e., females 60 or older and males 65 or older) received 32% of all minor tranquilizer prescriptions and 51% of all prescriptions for nonbarbiturate hypnotics and sedatives, although they represented only 9% of the population (or 17% of the adult population, who are most likely to receive prescriptions of this type). Carmody et al. (156) reported a similar analysis of these data, for 1972 through 1975, which indicated that pensioners received 35% of all prescriptions specifically for benzodiazepines. (This figure agrees with NDTI data for the U.S. in 1986, as described above; 34% of prescriptions for benzodiazepine minor tranquilizers and hypnotics combined were issued to females 60 or older and males 65 or older.)

ii. Institutionalized elderly. A number of studies have examined the prevalence of use of antianxiety and hypnotic agents among the elderly in institutions, including hospitals (table 26) as well as nursing homes and other long-term care facilities (table 27). As the tables indicate, studies in the U.S. generally show that, at any point in time during institutionalization, about 10 to 15% of the elderly receive prescriptions for anxiolytics [although Ingman et al. (510) found a rate of 20% in a long-term care facility in Connecticut in 1971], while about 15 to 25% received prescriptions for hypnotics. Most studies of the elderly in institutions in the United Kingdom indicate that about a third received prescriptions for hypnotics, although Mann et al. (707) found a rate of only 14% in long-term care facilities in London as well as in New York City.

In reviewing data of this kind, it is important to recall

TABLE 26

Prevalence of use by elderly in hospitals (based on surveys of medical records)

Study	Sample	Locality	Date of survey	Period in which drug was used	Type of drug	Age group	% using
Fracchia et al., 1973 (311)	Long-term male psychiatric patients of one hospital (n = 89)	U.S.A.: Central Joliet, NY	(Not stated)	Current use (?)	Minor tranquilizers	Below 59 60+	14.6 14.3
Prien et al., 1975 (892)	Elderly psychiatric patients of 12 Veterans Administration hospitals (n = 1,276)	U.S.A.*	1974	1 day	Anxiolytics	60+ (60–65) (66–75) (75) 60+	10 (14) (9) (8) (5)
					(Chlordiazepoxide)		(3)
Prien, 1975 (890)	Elderly patients of 12 Veterans Administration hospitals (n = 2,485)	U.S.A.*	1974	1 day	Anxiolytics	60+ (60–65) (66–75) (75)	9 (13) (9) (8)
Salzman and Van der Kolk, 1980 (967)	Elderly patients of a general hospital (excluding psychiatric and diabetic patients) (n = 195)	U.S.A.: Boston, MA	1978	1 day	Anxiolytics (Diazepam) Hypnotics (Flurazepam)	60+	11.3 (9.2) 22.6 (20.0)
Gosney and Tallis, 1984 (373)	General medical and geriatric medical elderly patients of a teaching hospital (n = 604)	United Kingdom: Liverpool	1983	1 mo (Rx)†	Hypnotics or sedatives	65	35.6
Magni et al., 1985 (694)	Sample of medical patients of a geriatric hospital	Italy: Padua	1983	Rx during hospital stay	Benzodiazepine anxiolytics Hypnotics	60	18.5 16.0

* American Lake, WA; Bay Pines, FL; Bedford, MA; Jefferson Barracks, MO; Little Rock, AR; Palo Alto, CA; St. Louis, MO; Seattle, WA; Sepulveda, CA; Wadsworth, CA.

† Rx, prescription(s).

that such prescription statistics do not necessarily measure actual consumption. For example, many or most of the studies shown in tables 26 and 27 report prevalence based on standing prescription orders, of which many may have been issued on a "prn" (as needed) basis. Ingman et al. (510) reported that 66% of such prescriptions for drugs acting on the CNS were not actually administered during the day of their survey. Similarly, Bergman et al. (65) found that the numbers of doses of psychotropic medications actually administered to patients of a Swedish university hospital were substantially less than the numbers prescribed.

Tables 26 and 27 do suggest, however, that elderly patients in institutions may be more likely to use hypnotics than elderly people outside of institutions. Similarly, Hendriksen et al. (459; also see table 25), who studied a random sample of elderly inhabitants of a suburb of Copenhagen, including residents of nursing homes as well as people living in their own homes, found that 41% of those in nursing homes used hypnotics regularly, as opposed to 24% of those living at home. Gilleard et al. (359) recorded the current prescriptions of new admissions to 25 homes for the elderly in a region of Scotland and found that 29% of those admitted from the community, versus 50% of those admitted from hospitals, were using hypnotics at the time of admission. Morgan (784) reviewed the literature on the use of hypnotics by the elderly and also concluded that the prevalence of use was higher among those in institutions than among those in the general community.

b. DURATION OF USE. The national surveys of physicians and prescriptions discussed above provide no direct information about the duration of benzodiazepine use by individual patients. However, NDTI data (508) indicate that in 1986 69% of prescriptions for benzodiazepine minor tranquilizers and 65% of prescriptions for benzodiazepine hypnotics were repeats of previous prescriptions issued to the same individuals.

This helps to explain an important apparent discrepancy in the data reviewed above. To take the U.S. as an example, in 1981 persons aged 65 or older represented about 10% of all those who had used an anxiolytic or

TABLE 27

Prevalence of use by elderly in long-term care institutions (based on surveys of medical records)

Study	Population	Location	Date of survey	Period of reported use	Drugs	Age	% of population receiving Rx*	Other characteristics
Ingman et al., 1975 (510)	Residents of a long-term care facility for the elderly (n =	U.S.A.: CT	1971	1 day	Anxiolytics Hypnotics	Not specified	19.9 25.2	
James, 1985 (521)	Residents of 5 nursing homes (n = 764)	U.S.A.: Denver, CO	1983	Past mo	Benzodiazepines prescribed for use at bedtime	Av. age: 74 for females, 76 for males	10.4	
Mann et al., 1984 (707)	Probability sample of elderly residents of long-term care facilities in two cities (n = 95 in New York City and 159 in London)	U.S.A.: New York City; United Kingdom: London	(Not stated)	Current prescription	Minor tranquilizers Hypnotics	65+	12.0 13.0 14 14	New York London New York London
Morgan et al., 1982 (785)	Residents of 23 homes for the elderly (n = 1,154 in 1980 and 1,122 in 1981)	Scotland: Lothian Region	1980; 1981	1 day	Hypnotics (nitrazepam)	Not specified	33.5 34.0 (11.3)	1980 1981
Gilleard et al., 1984 (359)	Residents of 25 homes for the elderly (n = 1,114)	Scotland: Lothian Region	1983	Current prescription on admission	Hypnotics (nitrazepam) (temazepam) (triazolam)	Not specified	35.9 (2.6) (9.8) (7.8)	
				1 day	Hypnotics (nitrazepam) (temazepam) (triazolam)		35.0 (4.8) (7.9) (4.2)	

* Rx, prescription(s).

sedative medication within the past year (table 24), whereas these patients accounted for about 25% of all prescriptions for these agents (588, 508). This discrepancy suggests that a disproportionately high percentage of the elderly patients who received prescriptions for these drugs obtained relatively frequent repeat prescriptions for them. This interpretation is consistent with data from a number of studies indicating that older patients are particularly likely to use anxiolytics and hypnotics regularly for long periods.

Previous sections of this review (V D 2 a; V E 4; V E 5, c and d) have described studies finding that the prevalence of long-term regular use of anxiolytics and hypnotics tends to increase with age (e.g., refs. 1169, 848, 262, 936, 222, 1151, and 798). This finding has been reported for periods when the barbiturates predominated among medications used for these purposes, as well as in later studies, when the benzodiazepines were the most commonly prescribed anxiolytics and hypnotics.

In a report of a 1979 U.S. national-sample survey of the use of various psychotherapeutic drugs, Mellinger et al. (755) noted that the most striking difference between long-term and other users of anxiolytics was that long-term users tend to be older; 71% of all those who had used these drugs regularly for 1 yr or longer were aged 50 or older, and 33% were 65 or older.

With respect to long-term use of hypnotics in the elderly, in addition to the studies cited above that were

discussed in preceding sections of this review, Morgan (784) has reviewed a number of studies indicating that older patients are particularly likely to use hypnotics regularly on a long-term basis.

c. RELATION OF PRESCRIBED DOSAGE TO AGE. There are some indications that physicians tend to prescribe lower doses of benzodiazepines for older patients. An analysis (545) of NDTI data for 1984 indicated that prescriptions for diazepam written by U.S. office-based physicians for males under 65 specified a median daily dose of 15.3 mg, as opposed to 11.4 mg for older male patients; diazepam prescriptions for females under 65 had a median daily dose of 14.5 mg versus 9.9 mg for older females. The median daily dose of flurazepam for males under 65 was 26.7 mg versus 25 mg for older males, and the median daily dose for females under 65 was 26.7 mg versus 25.6 mg for older females.

These findings are supported by two surveys of prescriptions issued in family medicine centers [as described in more detail previously (section V D 2 a, page 339)], which found that prescriptions for benzodiazepines tended to specify lower doses for older than for younger patients. Prescriptions in a U.S. family medicine center called for median daily doses of 30 mg of chlordiazepoxide or 15 mg of diazepam for patients under 65 versus 20 mg chlordiazepoxide or 8 mg of diazepam for patients 65 or older (438). Similarly, in a Canadian family medicine center, diazepam prescriptions called for a median daily dose of 11.9 mg for patients 65 or younger versus 9.9 mg for older patients (936).

At least one study of hospitalized elderly patients provided findings consistent with those described above. Prien et al. (892) found that the doses of antianxiety agents prescribed for elderly patients of 12 Veterans Administration hospitals tended to decrease with age; those between 60 and 65 received a mean daily dose equivalent to 45 mg of chlordiazepoxide, whereas those over 75 received a mean daily dose equivalent to 33 mg of chlordiazepoxide.

d. CONCOMITANT USE OF MULTIPLE DRUGS. NAMCS data for 1980 and 1981 indicate that, at office visits by patients 75 or older with a mental disorder diagnosis, physicians prescribed an average of 2.6 drugs, as compared with an average of one drug prescribed at all office visits by all patients (585); 38% of visits by these patients resulted in the prescription of one psychoactive drug, and 35% resulted in the prescription of two or more psychoactive drugs. The report did not indicate the frequency of specific psychoactive drug combinations. It is of interest, however, that the two most common diagnoses for these patients were depression (35.4% of visits) and anxiety (26.2%) and that the two most frequently prescribed drugs at these visits were amitriptyline (15.3% of visits) and diazepam (10.2%).

The most direct information available on multiple drug use among elderly benzodiazepine users comes from studies of elderly patients in institutions. Morgan et al. (785) examined the records of all residents of local authority nursing homes in a region of Scotland who received a hypnotic on a given day; 57.6% of the hypnotics prescribed were benzodiazepines. He found that 26.2% of these residents also received another psychotropic agent on that day; the other drugs involved included phenothiazines (10.5%), analgesics (4.7%), antidepressants (4.5%), benzodiazepine anxiolytics (3.1%), and anticonvulsants (3.1%).

Salzman and van der Kolk (966) found that, among elderly patients of a general medical-surgical hospital who were receiving antianxiety agents, 38.5% were also receiving neuroleptics, 42.9% were also receiving tricyclic antidepressants, and 100% were also receiving flurazepam. Of patients specifically receiving diazepam, 67% also received nonnarcotic analgesics and 9% also received narcotics. Salzman (962) attributed these high rates of multiple drug use to the severity of the illnesses of the patients studied. Other studies have also found combinations of anxiolytics and neuroleptics among institutionalized elderly, though with much less frequency; for example, Kalchthaler et al. (551) found that, of a sample of residents of a nursing home, 13% received both minor tranquilizers and hypnotics, and 3% received both major and minor tranquilizers.

There have been a number of studies of multiple drug use among hospitalized elderly psychiatric patients. Prien et al. (892) found that, of elderly inpatients of 12 Veterans Administration hospitals, including both psychiatric and other patients, 77% were receiving multiple drugs of some kind, and 38% were using at least four different drugs simultaneously. Of patients whose primary diagnoses were of mental illnesses, 18% were concomitantly receiving two or more psychotropic agents; of the various psychotropic combinations, 21% combined an anxiolytic and an antipsychotic agent (893).

Fracchia et al. (310) studied elderly psychiatric patients of a state hospital and found that 24% of all patients were receiving a benzodiazepine minor tranquilizer in combination with at least one other psychoactive drug. The most common of these combinations was with an antidepressant or stimulant; 43% of patients receiving diazepam were also receiving imipramine. (This finding agrees closely with that of Salzman and van der Kolk, cited above.) They also found that 10% of the patients received a combination of an anxiolytic and an antipsychotic agent.

In a later study by Fracchia et al. (309), these investigators explored the common assumption that psychotropic combinations were employed so that smaller doses of each individual agent could be used. They surveyed drug use for 1 mo in 2,301 elderly long-term psychiatric inpatients and found that doses of psychotropics prescribed in combinations were actually higher than those specified when these drugs were prescribed alone. The average total daily dose of diazepam when prescribed alone was 7.68 mg; when prescribed concomitantly with

another psychotropic agent, the average total daily dose of diazepam was 9.1 mg.

On the other hand, it is not clear that older patients are more likely than younger patients to receive multiple psychoactive drugs. Fracchia et al. (311) studied treatment regimens provided to a younger (<59 yr) and older (>60 yr) group of hospitalized male psychiatric patients with similar symptom patterns. Of the younger group, 29.5% received multiple psychoactive agents, as opposed to 17.8% of the older group.

e. SUMMARY. Cross-national survey data indicate that, on average, about 15% of the elderly populations of the countries that have been studied report that they use anxiolytic/sedative medications in the course of a year. Other data indicate that the elderly are particularly likely to use both anxiolytics and hypnotics regularly and for long periods, so that they account for a disproportionately large percentage of all consumption of these medications. Elderly patients in institutions use more hypnotics, but not more anxiolytics, than the noninstitutionalized elderly.

At least in the U.S., physicians tend to prescribe lower doses of benzodiazepine anxiolytics and hypnotics for older patients than for younger patients.

There are few sources of information on the prevalence of concomitant use of multiple psychoactive drugs among elderly outpatients. In the U.S., two or more psychoactive medications are prescribed at 35% of office visits by patients 75 or older who have diagnoses of mental disorder. Studies of treatment for elderly patients in institutions indicate that a substantial proportion of those who receive anxiolytics and hypnotics also receive other psychotropics. The data regarding the specific combinations used are not particularly consistent, probably because these practices vary across regions and institutions. Apparently anxiolytics are commonly prescribed together with antidepressants and not infrequently with neuroleptics.

2. Children. An extremely small percentage of benzodiazepine prescriptions is written for children, and there is very little information about this use. NDTI data indicate that children and adolescents (10 to 19 yr) received 1% of all prescriptions for benzodiazepine minor tranquilizers written by office-based U.S. physicians in 1986; less than 1% were issued for children younger than 10 (508).

A study of psychotropic prescriptions issued by a group general practice in Scotland for children under 12 found that a total of 336 such prescriptions were written for 2,845 patients in the course of 1971 (32). The report does not state how many of the children in the practice received these prescriptions. Most of these prescriptions were for behavior disorders or enuresis. Nitrazepam accounted for 6.3% of all psychotropic prescriptions; diazepam and chlordiazepoxide accounted for another 10.1%.

Fifty consecutive male and 50 consecutive female admissions (age 7 to 18) to a child psychiatric facility in Manitoba during 1976 and 1977 were studied by Ahsanuddin et al. (7). Diazepam was prescribed for 40% of the children diagnosed with depression. No benzodiazepine use was found in association with any of the other diagnoses.

3. Pregnant patients. Forfar and Nelson (307) interviewed a sample of 911 Scottish women (two thirds from a large city and one third from a small country town), who had recently given birth, about their use of drugs during pregnancy. The interview data were confirmed by examination of medical records as well as National Health Service prescription records. The date of the survey was not given, but must have been in the late 1960s. Tranquilizers (type not specified) were taken by 1.4% of the women during the first trimester and by 3.6% during the whole of pregnancy. Hypnotics (type not specified, though probably at this date including barbiturates) were taken by 0.1% during the first trimester and by 1.4% during the whole of pregnancy. Tranquilizers and hypnotics were used for a mean duration of 23 days during pregnancy.

Brocklebank et al. (133) studied the records of a cohort of 2,528 TN Medicaid recipients who had given birth during a 1-yr period between 1975 and 1976. Six % had received diazepam at some time during pregnancy. Both diazepam and codeine (not necessarily concurrently) had been taken by 2.7% of the women; diazepam and barbiturates by 1.3%; and diazepam, codeine, and barbiturates by 0.9% at some time during pregnancy. Among women whose prepregnancy records were also studied, and who had used diazepam before pregnancy, slightly fewer continued to use it during pregnancy. These authors also described a number of other studies of drug use among pregnant women, which found that use of various tranquilizers (types not specified in this report) during pregnancy ranged from 4 to 21% of the subjects surveyed.

4. Mentally retarded patients. Data on drug use were collected as part of a national study of the characteristics of residential care for mentally retarded patients (463); the data were based on interviews with direct-care personnel of both private community facilities and public institutions, selected to be nationally representative of residential facilities for care of the mentally retarded in the U.S. The interviews were conducted in 1978 and 1979, and they pertained to 962 randomly selected residents of community facilities and 992 randomly selected residents of public facilities. It was found that psychotropic drugs were regularly prescribed for 26% of the community facility residents and for 38% of the public facility residents. Benzodiazepine anxiolytics (chiefly diazepam) were prescribed for 3.2% of the community facility residents and for 4.2% of the public facility residents.

When compared with these national data, data from a study conducted in MO (513) suggest that there may be considerable geographical variation in the extent of benzodiazepine use in such institutions. This study, based

on client records as well as interviews with case managers, sampled 295 randomly selected residents of MO's community and public residential facilities for the mentally retarded; the date of the survey was not specified. The data indicated that 5% of community facility residents and 17% of public institution residents (a statistically significant difference) received prescriptions for minor tranquilizers, chiefly diazepam; flurazepam was prescribed as a hypnotic for 2% of the community facility residents and for 3% of those in public facilities. In some instances, minor tranquilizers were prescribed in combination with major tranquilizers. Statistical analyses indicated that minor tranquilizer use was significantly associated with clients' level of medical-physical problems (for control of seizures and as a muscle relaxant for patients with other physical problems), rebellious behavior, and stereotypic behavior. The authors noted that the use of the minor tranquilizers for controlling rebellious behavior, if that was indeed the reason for this use, is of questionable efficacy and can even exacerbate such behavior.

Tu (1091) conducted a survey of 2,238 residents of 5 public residential facilities for the mentally retarded in Eastern Ontario; the data were collected by means of questionnaires completed by direct care personnel in 1975 and 1976. The study found that diazepam was provided for 3.8% of the patients, chlordiazepoxide for 1.7%, and flurazepam for 0.8%. The report states that most psychotropic medications were prescribed for long periods of use, but it does not specify the duration of prescriptions for individual drugs or drug groups. Minor tranquilizers were provided more frequently for epileptics than for nonepileptic patients. Minor tranquilizer and major tranquilizer combinations accounted for 10% of all psychotropic drug combinations.

G. Surveys of Misuse and Recreational Use

The epidemiological research considered above has pertained primarily to legitimate use of benzodiazepines. The following section considers studies of misuse and recreational use of these drugs and of the consequences of such misuse. The distinctions among these types of drug self-administration have been described using terms whose meanings are often poorly defined in individual studies, and which apparently have different meanings for different authors.

We use the term *recreational use* to refer to instances of drug taking in which the action of the drug reinforces and thus serves to maintain the drug-taking behavior. (For a discussion of reinforcement as an integral component of drug-seeking, see section II A, page 254.)

Much of the literature on inappropriate use of benzodiazepines pertains to use of these drugs that is outside of or contrary to medical instruction, but is clearly distinct from drug-taking behavior maintained by the drugs' reinforcing effects. We refer to this type of use as *misuse*, which we define as self-administration of a drug obtained without a prescription or other medical authorization, or in a manner deviating from medical instructions or from accepted medical opinion regarding appropriate therapeutic use (but excluding recreational use); thus, misuse would include an individual's consumption of a drug for self-treatment of anxiety, when the drug was obtained without a prescription for that individual.

These definitions are offered here to represent our perspective in evaluating the research reviewed. However, in describing reports whose authors have used these terms differently, or have used different terms (e.g., "abuse"), we have generally retained the authors' terminology and have included their definitions where needed.

In considering this research, it should be noted that estimates of the prevalence of misuse in the populations studied have often been based on self-reports or histories with or without laboratory confirmation. Also, methods for detection and measurement of benzodiazepines have changed considerably since these drugs were introduced; thus, the incidence of detection of a given drug may increase over time because of improvements in analytical techniques, independent of changes in the frequency of misuse; and the specific methods employed have also varied across regions and testing facilities. Some programs screen only for certain drugs of the group; and, in general, individual compounds are more likely to be detected if they have longer half-lives (because testing is often delayed) and if they are of relatively low orders of potency (since these therefore require higher doses, thus increasing the amount of drug available for detection).

1. Prevalence and patterns of misuse. For an excellent and interesting review of surveys of drug misuse and recreational use among the general populations of a number of countries, as well as a valuable consideration of the methodology of such research, the reader may wish to refer to Johnston (539).

a. SURVEYS OF THE GENERAL POPULATION. In a 1981 interview survey of a national sample of the U.S. population, as described previously, Mellinger and Balter (752) found that 2% of all men and 2.3% of all women between 18 and 79 yr of age reported that, within the previous year, they had used prescription antianxiety medications that they had obtained without appropriate prescriptions; only 0.1% of the population reported such misuse for a total of 30 days or more during the year. Also, 0.4% of men and 0.9% of women had used inappropriately obtained prescription hypnotics; virtually none of this use was for more than 30 days during the year.

In 1980, Ladewig et al. (624) sent a questionnaire to all practicing physicians in Switzerland asking about abuse of benzodiazepines among their patients; abuse was defined as "unauthorized use of drugs in the absence of an appropriate indication or, where an indication exists, intake of doses in excess of those required for therapeutic purposes." Of the 5,415 (73%) physicians who responded, 1,123 reported observations of some form of benzodiazepine abuse. In telephone interviews with

these physicians, 435 were able to document cases of inappropriate use or dosage increases in a total of 794 patients. Of these, 22.7% appeared to have abused benzodiazepines alone; 30.2% had abused benzodiazepines together with alcohol or another drug; 25.6% were cases where abuse was not certain or insufficiently documented; and 14.9% of these cases of suspected abuse appeared to the investigators to have been appropriate treatment. The investigators found that the relative frequency with which specific benzodiazepines were abused corresponded to the relative frequency of their overall legitimate use in the population. On the basis of these data, the investigators estimated that "two new abuse cases can be expected for every 100,000 prescriptions."

A series of studies in Sweden by Boethius and Westerholm (98–100), described in detail on page 333 above, examined patterns of individuals' purchases of psychotropic drugs (chiefly benzodiazepines) over 5-yr periods. While most individuals significantly decreased such purchases over time, 15 (0.6%) of 2,566 patients developed regular purchase patterns, and 4 (0.0015%) showed indications of overuse or abuse, including increasingly frequent purchases and simultaneous use of prescriptions from different physicians (100).

The largest number of general population surveys of abuse of various psychoactive drugs pertains to drug use among students and other youth. Most of these surveys have collected information on self-reported use of illicit substances and "nonmedical" use of prescription drugs, which is usually defined as use of such drugs without medical prescription or authorization. Most have used questionnaires and, in many cases, have collected data on use of "tranquilizers" without attempting to specify types of tranquilizers. Following are brief descriptions of some of these surveys, as reported from different countries; these are presented as illustrative of this fairly extensive body of literature. These descriptions summarize only the findings relevant to benzodiazepine use, although the psychoactive drug use most prevalent among virtually every population of youth is of illicit substances.

Two regular, ongoing surveys sponsored by the National Institute on Drug Abuse have examined nonmedical drug use among youth in the U.S. One is an annual questionnaire survey of nonmedical use of licit and illicit drugs that has studied nationally representative samples of high school seniors and of youths graduating from high school (540). As indicated in table 28, this survey found that nonmedical use of tranquilizers among high school seniors peaked in 1977 and has since substantially declined. In 1985, 5.5% of young adults, i.e., those who graduated from high school 1 to 8 yr previously, reported nonmedical use of tranquilizers in the prior year; 1.8% reported such use in the prior month. Of college students who had graduated from high school 1 to 4 yr previously, 3.5% had used tranquilizers in the prior year (as opposed to 6.9% in 1980), and 1.4% had used them in the prior month (as opposed to 2.0% in 1980). Among both the young adult and the college student samples, there was virtually no reported nonmedical use of tranquilizers on a daily basis.

TABLE 28

Use of tranquilizers by high school seniors in the U.S. [based on Johnston et al., 1986 (540)]

	1977	1985
Percentage who ever used	17.0	11.9
Percentage who used in past yr	10.8	6.1
Percentage who used in past mo	4.6	2.1

The National Household Survey on Drug Abuse (762), sponsored by the National Institute on Drug Abuse, found that, in 1982, 4.9% of the population between 12 and 17 yr of age reported ever having used tranquilizers without a prescription, as did 15.1% of those between 18 and 25, and 3.6% of those 26 or older.

In a questionnaire survey of drug use among university students in MD (1025), it was found that 15.5% of male and 25% of female freshmen had ever used tranquilizers, whereas 31% of male and 30% of female upperclassmen had used tranquilizers. The 7.6% of freshmen who reported some continued use of these drugs included 5.1% who reported use daily or every other day and 2.5% who reported that they used tranquilizers about once a month. The 5% of upperclassmen who reported some continued use included 1% who reported daily use, 1% who reported weekly use, and 3% who reported use about once a month.

In 1969, 6% of students in grades 7 through 12 in Halifax, Nova Scotia, reported that they had used tranquilizers in the previous 6 mo; in 1970, such use was reported by 7% of the students (1137). In 1968, 9.5% of Toronto high school students had used tranquilizers during the prior 6 mo, as opposed to 9.0% in 1974; most of the students reporting such use had used these drugs only once or twice in the 6 mo (1018).

Smart et al. (1020) reported the results of a household interview survey of drug use among students and other youth in India (ages 10 to 24, in urban and rural areas in and around Chandigarh), Mexico (ages 12 to 25, in a low-socioeconomic area south of Mexico City), and Canada (ages 14 to 25, in an area of Ontario east of metropolitan Toronto). The report did not specify when the survey was conducted. In all three countries, tranquilizers were the third most frequently used psychoactive substances (after cannabis and amphetamines). The findings pertaining to tranquilizer use are summarized in table 29.

A questionnaire and interview study of 20-yr-old male students of 31 military schools throughout Switzerland found that 3% had taken hypnotics or tranquilizers; 0.5% had taken such drugs more than 6 times (52). These rates apparently refer to lifetime experience.

Nonmedical use of tranquilizers was reported by 11.3% of male and 4.1% of female university students (total prevalence = 7.8%) in Delhi, India; 90% of these students

TABLE 29
Tranquilizer use among youth of three countries [based on Smart et al., 1981 (1020)]

	India		Mexico		Canada	
	Students	Other	Students	Other	Students	Other
Ever used	6.1	1.5	2.4	10.4	6.2	6.9
Used in past yr	3.6	1.0	0	1.5	2.7	1.7
Used in past mo	0.7	0.5	0	0.7	0.8	0.6

reported that they used the drugs once a month or less (777). Among medical and other postgraduate students in the state of Uttar Pradesh, surveyed in 1975-1976, 7% had used chlordiazepoxide (5% less than once a month), and 2% had used diazepam (1% less than once a month) (248). In Lucknow, 1.3% of male college students had used minor tranquilizers at some time (1003), as had 13.5% of medical students (1002); the latter included 9.5% who used tranquilizers about once a month, and 2.7% who used them about 2 or 3 times a month.

A 1974 survey of high school and college students in five cities in the Philippines (1209) found that 8% used diazepam, 4% lorazepam, 3% chlordiazepoxide, and 3% nitrazepam. Some of this use was apparently of more than one of these drugs, so that the total prevalence of use of benzodiazepines was probably less than the total of these percentages. It is not clear from the report whether these figures pertained only to nonmedical use or whether medical use may have been included. Also, the report implies but does not specify that the reported use was of a continuing pattern.

Among male students of a university in Christchurch, New Zealand, in 1970, 13.8% reported nonmedical use of sleeping pills and 9.2% of tranquilizers (924). These rates apparently referred to lifetime prevalence of use.

Minor tranquilizers had been used more than once in the prior 3 mo by 2.4% of secondary school students in Zambia. Of a sample of other students in a variety of educational institutions in the country, 9% of males and 3% of females had ever used tranquilizers, chiefly diazepam (444).

Relatively high rates of use of benzodiazepines were reported in a questionnaire survey of university students in Benin City, Nigeria (810). The date of the survey was not reported. The study apparently did not specifically distinguish medical and nonmedical use, but the report implied that most of the use among these students, as among other Nigerians, was nonmedical. There was considerable variation in rates of response to specific questions. Of those who provided responses to the relevant questions, 58% of males and 53% of females had ever used diazepam or chlordiazepoxide; 6% of males and 5% of females had ever used nitrazepam. Twenty-four % reported some continuing use of diazepam or chlordiazepoxide, of whom 50% used them several times a month, 10% used them 2 to 3 times a week, 31% once a week, and 9% used them daily. The investigator comments that diazepam and chlordiazepoxide appear to be used without prescriptions with some frequency among urban Nigerians in general, who take "a very casual attitude" about use of these drugs.

Among university students in Sao Paulo, Brazil, 21.8% had ever used tranquilizers (1208). "Frequent" use of tranquilizers was reported by 2.5% of high school students in Santiago, Chile (1105).

In summary, there appears to be little misuse of the benzodiazepines among the general population. Among adults and youths who do misuse benzodiazepines, the evidence appears consistent that this misuse is on an occasional and relatively infrequent basis; it is probably inconsequential. There is no evidence that these incidents of self-administration evolve into a pattern of significant misuse by even a small proportion of the population.

b. STUDIES OF DRUG ABUSERS. Tyler and Frith (1093) found that, of 51,390 women admitted to U.S.-funded drug abuse treatment clinics (in a 12-mo period, date not specified), 4% reported tranquilizers (type not specified), and 3% reported other nonbarbiturate sedatives as their primary drug of abuse. The significance of such self-reports of drug preference is obscure. The report also provided no indication whether the reported drug use was confirmed by laboratory analyses.

Drug abuse or dependence (as defined by the WHO) was claimed in 7% of all inpatients of a psychiatric hospital in Munich, Germany, between May 1980 and December 1982 (1167). It is not clear how the definitions of abuse or dependence were implemented to arrive at these diagnoses. Benzodiazepines (chiefly diazepam, bromazepam, and lorazepam, in that order) were abused by 77% of these patients. Among benzodiazepine abusers, 30% abused benzodiazepines alone, and 70% abused benzodiazepines in conjunction with other drugs.

Busto et al. (149) studied the patterns of drug abuse in 163 patients referred to the clinical facility of Toronto's Addiction Research Foundation specifically for treatment of benzodiazepine abuse; benzodiazepine use was confirmed by analyses of urine (thin-layer chromatography, or TLC) and plasma (high-performance liquid chromatography). Fifty-six % had used only benzodiazepines, and 44% had used multiple drugs; diazepam was the most frequently abused drug in both groups. The investigators found that 28% of the benzodiazepine-only group, as opposed to 68% of the multiple-drug group, had increased their dosages of benzodiazepines. Seventy-one % of the benzodiazepine-only group, as opposed to 37% of the multiple-drug group, reported that they had been unable to stop their drug use because of withdrawal symptoms. The median daily dose taken by the benzodiazepine-only group was equivalent to 15 mg of diazepam, whereas that taken by the multiple-drug group was equivalent to 40 mg of diazepam.

The criterion for "abuse" used by these investigators (149) included a cumulative measure of benzodiazepine

consumption, as specified in total diazepam-equivalent doses. They argue that individuals who extend therapeutic use of anxiolytic medications beyond a certain time period are abusing these drugs. While a definition this explicit has its virtues, it is debatable that an extension of drug use beyond a period that some consider medically appropriate should necessarily be considered as abuse. It is also debatable and moot whether benzodiazepine abuse can be distinguished on the basis of whether or not users increase their dosages (especially when such increases, as reported in this study, do not exceed the recommended therapeutic range); as this study suggests, the concomitant use of other drugs might differentiate abusers more effectively than does increasing dosage.

Two laboratories in Norway have reported results of urinalyses (Enzyme Multiplied Immunoassay Technique, or EMIT) conducted in 1981 through 1983 for various populations, chiefly of psychiatric and drug abuse treatment facilities. Benzodiazepines were detected in 8% (686) or 17% (951) of the samples analyzed; unfortunately, neither report specifies what proportion of the populations sampled proved positive for benzodiazepines.

i. Studies of opiate abusers. A study of patients treated for narcotic dependence at the NIMH Clinical Research Center in Lexington, KY, indicated that abuse of and dependence on sedatives among such addicts had increased substantially between 1957 and 1966 (160). Of the sedatives that were specified, those abused in 1957 were exclusively barbiturates, while those in 1966 included nonbarbiturate hypnotics, though not benzodiazepines. By the mid-1970s, however, 5 of 40 heroin addicts in a treatment program in Seattle claimed that the drug they had used most frequently in addition to heroin was diazepam (906). Of 427 patients admitted to programs in five geographical areas of the U.S. for treatment of drug abuse (chiefly opiates) in 1978, 29.5% reported nonmedical use of diazepam in the prior year, 8.4% of chlordiazepoxide, and 4.4% of flurazepam (134). Those mentioning use of diazepam represented 81% of all patients reporting use of any stimulants or depressants. Of 89 patients reporting use of such drugs in the previous month, 42 (49%) named diazepam as the drug they would prefer to use if all such drugs were equally available; this was by far the highest percentage of all choices.

Sixty-two of 65 heroin addicts treated at three day-care centers in the United Kingdom in 1969 reported abuse of barbiturates, but no use of nonbarbiturate sedatives was reported (773). However, of 100 consecutive addicts attending a London drug dependency clinic 10 yr later, 39 reported abuse of benzodiazepines, while only 20 were abusing barbiturates (525).

ii. Studies of methadone patients. Kokoski et al. (593) reported the results of urine screening (TLC) of patients in five programs for treatment of narcotic abuse. Of patients in a methadone maintenance program in KS, 5% of specimens were positive for benzodiazepines, as opposed to 18 to 43% of specimens from patients in various methadone maintenance programs in MD. Benzodiazepines were also detected in urines of 4 and 10% of patients in abstinence programs in MD. The investigators speculated that the higher rates of benzodiazepine use among methadone patients, as opposed to abstinence patients, might be due to some specific drug interaction effect sought by the methadone patients.

Woody et al. (1173) interviewed 77 methadone maintenance patients in Philadelphia between November 1973 and January 1974. They found that the only drug used by prescription by a substantial proportion of these patients (21%) was diazepam; another 29% obtained diazepam illicitly. The investigators commented that some of this use of diazepam might have been for treatment of psychiatric symptoms prevalent among this population.

Kleber and Gold (583) noted a marked increase in the use of diazepam among methadone maintenance patients during the 2 yr prior to their report (published in 1978). Problems associated with diazepam use had led to hospitalization for eight patients, who had been using doses of diazepam as high as 50 to 225 mg per day. Patients claimed that diazepam was used in doses of 25 mg, or preferably 50 mg, to "boost the high" associated with administration of methadone. The investigators remarked that tolerance to diazepam apparently developed quickly in this population and that there had been a number of striking interaction effects, e.g., daytime sleeping, psychomotor decrements, and pathological rage attacks. However, they also found that flurazepam was prescribed as a hypnotic in this population with no evidence of abuse.

During 3 mo of 1977, Budd et al. (143) analyzed over 8,500 urine specimens (some multiple specimens from the same individuals) from 7 methadone clinics in Los Angeles County; specimens were screened by EMIT, and analyses were confirmed by TLC. They found considerable month-to-month variation within clinics with respect to the proportions of specimens positive for diazepam, as well as substantial variation among clinics, ranging from 4.9 to 48.6% of diazepam-positive specimens. As the investigators noted, "These variations [among clinics] may reflect use by legitimate prescription, clinic diazepam use policy to enhance the effects of methadone at preventing withdrawal symptoms, local illicit availability of the drug, and/or preferences for the drug due to various sociological factors associated with the particular clinic population." The report also described findings of urine screenings for the County's probation department; despite the variations in findings for the methadone clinics, the extent of diazepam use in all methadone clinics was equal to or greater than that found among probationers.

Radioimmunoassay (RIA) techniques for the detection of benzodiazepines in urine became available in 1977; Kaul and Davidow (569) found that RIA detected a much larger number of benzodiazepine-positive specimens

than could be detected by TLC. They reported that, between 1977 and 1979, RIA demonstrated the presence of benzodiazepines in 11 to 17% of urines from a large sample of methadone patients in various New York City treatment programs.

However, urinalyses conducted using TLC detected benzodiazepines in 65% of patients enrolled in a Philadelphia methadone clinic and 70% of patients in a Baltimore methadone clinic in 1979 and 1980 (1048). These patients reported diazepam as the drug they most frequently used and a median daily dose of 40 to 45 mg; 60% of diazepam users reported having used doses of over 100 mg. They used the diazepam shortly after their daily methadone maintenance dose to "boost" the effect of methadone. The same patients reported that barbiturates did not augment the subjective effects of methadone. The same group of investigators (1047) were able to reduce supplemental diazepam use by rearranging clients' privileges associated with methadone receipt or by directly paying the clients when their urine specimens were free of benzodiazepines.

Leifer et al. (643) studied 100 women who had been admitted to a drug abuse treatment program in Philadelphia between 1978 and 1981, who were maintained on methadone, and who remained in the program long enough (minimum, 4 mo) for the investigators to obtain at least 20 urine specimens; specimens were analyzed by TLC. Urinalyses indicated that 98% of the women abused other drugs at some time during the study. Ninety % gave at least one specimen positive for benzodiazepines, and for 68% of the women at least 20% of specimens were positive for diazepam. The investigators were surprised to find a highly significant positive association between the dose of methadone and the average percentage of urines per patient positive for diazepam. They speculated that this association might be explained by the patients' propensity to use diazepam for self-treatment of anxiety or that diazepam might increase the amount of methadone that reaches the CNS.

Tennant et al. (1079) found that plasma levels of methadone 24 h after an 80-mg dose were substantially lower (average, 102 ng/ml) in methadone maintenance patients who abused diazepam, heroin, or alcohol than in such patients who did not (average, 410 ng/ml). They speculated that abuse of these drugs among methadone maintenance patients may be due to interindividual differences in metabolism of methadone, such that some individuals do not get enough methadone to "hold" them between maintenance doses. It might be noted, however, that the observed difference in methadone plasma levels might be explained in other ways; for example, it is possible that the other drugs used by these patients might alter methadone metabolism.

Preston et al. (889) examined the effects of single doses of diazepam (20 and 40 mg) in patients maintained on 50 to 60 mg of methadone daily who had histories of diazepam abuse. They found that the combination of increments of methadone and diazepam produced significantly greater effects on subjective measures and pupil diameter than were produced by either drug alone or their additive effects. The drug combination was identified more frequently as a benzodiazepine than as methadone.

iii. Studies of alcoholics. In 1973 Freed (318) reviewed numerous earlier studies indicating that patients dependent on alcohol frequently used or abused other drugs, especially barbiturates and other sedatives. A recent review (163) of research on the effects of concurrent use of alcohol and benzodiazepines concluded that "epidemiological information is lacking on the true extent of the combined abuse and on the patterns and prevalence of use of these two drugs."

Interviews with 293 women admitted to an alcohol detoxification facility in the U.S. in 1976 indicated that 57% had taken hypnotics or antianxiety drugs (not further specified) (984). Twenty-nine % had abused hypnotics or anxiolytics, according to a definition of abuse that entailed "the occurrence of a major life problem related to the use of a substance. . . ." Of the 29% thus identified as abusers, 80% had obtained these drugs by prescription. The study found that the alcoholics who had abused any other drugs, i.e., as well as alcohol, had more severe alcoholic histories than those who had not.

Busto et al. (151) studied 216 consecutive outpatients referred for treatment of chronic alcoholism in Canada between June and July of 1981. Benzodiazepines were detected in the urines of 33% of these patients (48% of women and 28% of men) versus none detected in a control group of patients undergoing medical assessment and versus 4 to 6% in the general population. Of those positive for benzodiazepines, 54% had obtained the drugs by prescription. Benzodiazepines had been used most frequently for anxiety (in 53%) and, occasionally, for self-treatment of alcohol withdrawal symptoms (10%). Fifty-four % of those positive for benzodiazepines were considered abusers, in that they obtained the drugs without prescriptions or took large doses.

Wiseman and Spencer-Peet (1161) conducted interviews with and obtained urinalyses (gas chromatography and immunoassay) for 107 patients admitted to an alcohol treatment facility in the United Kingdom. In the 2 wk prior to admission, 76% had been using other drugs, most frequently benzodiazepines, which had been used by 41%. Eight % of the other drugs used had been obtained by prescription; the report did not specify which other drugs had been obtained by prescription.

c. STUDIES OF CRIMINALS AND CRIMINAL ACTIVITY RELATED TO BENZODIAZEPINE USE. A series of reports by Budd and coworkers has described the results of urinalyses conducted for the Los Angeles County Department of Probation. The findings pertain to the proportions of samples submitted for analysis that prove positive for the presence of a number of substances, including diazepam. Multiple specimens may be provided

for the same individual. In the case of prescription drugs, positive findings may include some percentage of drugs prescribed by physicians. Screening for diazepam or its metabolites is conducted by EMIT and confirmed by TLC. Of 17,545 samples submitted by the probation department in 3 mo of the Spring of 1977, 4.9% were positive for diazepam; of these positive samples, 65% were positive for diazepam alone, while 22% were also positive for morphine or codeine, 15% were also positive for barbiturates, and 5% were also positive for an amphetamine (143). In another study, of 350 diazepam-positive samples analyzed for the presence of other drugs, 42% contained none, 17% codeine and/or morphine, and 15% methadone; of 115 cocaine-positive samples, 3% were also positive for diazepam (142). A third report from this laboratory (141) indicated that, of 10,000 probationers' samples analyzed in the first 2 mo of 1977, 1978, and 1979, diazepam was detected in 11.7%, 9.7%, and 10.0%, respectively.

In interviews with youths in two rehabilitation centers and a city jail in the Philippines, 67% reported that they used diazepam, 46% lorazepam, 44% nitrazepam, 40% oxazepam, and 21% chlordiazepoxide (1209).

Simonds and Kashani (1014) studied the relation of use of various drugs and violent crimes among 112 delinquent boys committed to a training school in the U.S. The subjects' drug use and abuse were assigned scores based on data obtained in interviews by a psychiatrist. Scores indicating the extent of use/abuse were compared with the numbers of offenses against property or persons. Significant positive correlations were found between the use of each of five drugs and offenses against persons; diazepam was one of these five drugs (which also included phencyclidine, barbiturates, cocaine, and amphetamines).

Shaffer et al. (1004) interviewed a sample of male narcotic addicts representative of those arrested by the Baltimore Police Department; they attempted to relate use of nonnarcotic drugs, during periods of active narcotic addiction and during periods of nonaddiction, to measures of the subjects' criminal activities. The nonnarcotic drugs most frequently used by blacks during periods of active addiction, in order of frequency of use, were marijuana, cocaine, barbiturates, and benzodiazepines; those used by whites during active addiction were cocaine, marijuana, barbiturates, amphetamines, benzodiazepines, and methaqualone. During periods of nonaddiction, the drugs most frequently used by blacks were the same as those used during periods of active addiction; those used by whites were marijuana, barbiturates, cocaine, benzodiazepines, amphetamines, hallucinogens, and methaqualone. Benzodiazepines appeared to be used more often by whites, but not blacks, during periods of active addiction than during periods of nonaddiction. Benzodiazepine use was positively correlated with illicit drug dealing among whites during periods of active addiction as well as periods of nonaddiction; it was negatively correlated with theft, as well as total days of criminal activity, among blacks during periods of active addiction. The investigators concluded that benzodiazepine use "was associated with increased criminal activity among Whites and lessened criminal activity among Blacks."

Hoover et al. (490) sent a questionnaire to the pharmacy directors of a representative sample of all U.S. short-term medical and surgical hospitals. Fifty-seven % responded to questions regarding thefts of controlled substances from these hospital pharmacies during 1979. With regard to substances under the Drug Enforcement Agency's schedules III, IV, and V, a total of 197 thefts was suspected and/or documented; these thefts involved 7,493 dosage units. Benzodiazepines (almost exclusively diazepam) were stolen in 50.7% of the thefts, representing 73.6% of the dosage units stolen.

On the basis of an examination of sales and prescription data, Bergman and Griffiths (67) found that the rates of legitimate use of oxazepam and diazepam in Sweden between January 1982 and June 1984 were roughly equivalent. However, reports of thefts or losses and of prescription forgeries involving diazepam were consistently more frequent than those for oxazepam over this period and across different geographical regions of the country. The authors claimed that this difference "confirms the hypothesis, derived from laboratory studies in humans and supported by epidemiological data from the United States, that diazepam has a greater abuse liability than oxazepam." However, the significance of this finding should be qualified by a number of relevant considerations. (*a*) The thefts/losses and forgeries reported (particularly since they occurred in only three urban areas) may not reflect independent phenomena; e.g., a large number of the incidents might have been perpetrated by or on behalf of a small number of people, and/or the proportions of actual "abusers" of diazepam and oxazepam might have differed from the proportions of thefts/losses and forgeries involving these drugs. (*b*) The absolute numbers of thefts and losses (135 reports for both drugs) and of prescription forgeries (476 for both drugs) over this 2.5-yr period were very small. (*c*) Great caution should be exercised in drawing conclusions from such data when only two benzodiazepines are compared, i.e., in the absence of any comparisons with substances known to have greater abuse liability (e.g., a barbiturate) or substances with no abuse. (*d*) The report does not specify whether these thefts/losses and forgeries involved diazepam or oxazepam alone, or whether they may have involved a number of drugs including diazepam or oxazepam. Studies of this kind may be of interest relative to assessments of abuse liability and should be undertaken, but they should provide more information, as suggested in the above comments, and they should take great care to avoid misinterpretations of the data presented.

d. SUMMARY AND DISCUSSION. Experimental studies

can apparently distinguish between normal subjects and sedative abusers on the basis of the reinforcing effects of benzodiazepines (as described in section II C, pages 261 to 267); that is, these effects can be detected much more readily in abusers. Apparently this distinction can also be demonstrated on epidemiological grounds, since the studies described above indicate that, relative to the general population, there is an increased prevalence of benzodiazepine use in various populations of abusers—including alcoholics, methadone maintenance patients, and perhaps also heroin abusers. This may reflect an increased prevalence of psychiatric symptoms among these populations, for which benzodiazepines may legitimately be prescribed, as well as an increased prevalence of recreational use.

A substantial proportion of methadone maintenance patients use diazepam. This may reflect a novel interaction, such as some enhancement of the effects of one of these substances by the other (889), that would predict perference for diazepam among this population; if there is such an interaction, it is apparently not pharmacokinetic (888). The specificity of this effect also remains to be determined. That is, some investigators appear to believe that the observed effects are specific to benzodiazepines, or particularly specific to diazepam; others feel they may be obtained with many or most sedatives. It should be feasible to explore whether, if other benzodiazepines were equally available, methadone-maintained subjects would in fact prefer diazepam. In any case, combined use of these drugs bears continued close scrutiny, both to attempt to establish causal factors for this use and to determine whether any particular risks may be associated with long-term use of this combination.

2. Surveys of drug overdose or drug-associated deaths. Studies of drug overdose suggesting misuse of drugs include surveys of hospitalizations due to ingestion of excessive doses of drug, surveys of reports from coroners on the incidence of drug-induced or drug-related deaths, and case studies of drug overdose. Surveys of hospital admissions resulting from overdose or of coroners' reports of drug-related or drug-induced deaths may not reflect cases exclusively of misuse, since they can include cases in which drugs are detected after ingestion of therapeutic doses as directed by a physician. In interpreting surveys of hospital cases and of coroners' reports, it should be kept in mind that these studies identify drugs that are detected in subjects regardless of whether the drugs are responsible for the fate of the subject. For example, emergency room tabulations of cases involving ingestion of more than one substance include each substance reported or detected, regardless of their relation to the patients' condition; thus the frequency of mentions of a given drug in such surveys is not a direct measure of the frequency of overdoses of that drug.

Instances in which subjects have ingested several drugs have been treated differently in various surveys. For example, some surveys of coroners' reports show incidences only for those drugs considered the primary agents involved in each case, while others report all substances involved. Further, different studies determine the agent or agents involved according to different methods. For example, in most instances coroners identify the "primary drug" responsible for overdoses according to concentrations in body tissues; as discussed previously (page 371), analytical techniques vary in their reliability and sensitivity for detection of benzodiazepines.

Although alcohol is clearly an important contributor in many overdose cases, it is not always considered in overdose surveys, probably because alcohol continues erroneously to be regarded as distinct from other behaviorally active drugs; thus, in some surveys, representation of a given drug class might appear higher than it would if alcohol were included. For example, Milla et al. (761) excluded 408 acute alcohol intoxications from their survey of emergency room cases; if all of these cases had been included, the percentage accounted for by benzodiazepine cases would have been 15%, rather than the 31% reported, and the percentage accounted for by barbiturates would have been 20%, rather than the 44% reported.

The present review examined only studies that listed benzodiazepines specifically. Many of the surveys listed prevalence by drug class rather than by individual agents. Studies that listed incidence of detection of anxiolytics or tranquilizers without further specification as to drug type were not reviewed, since these groups of drugs can include different drugs in different countries, and since many studies classify these drugs differently. For example, benzodiazepines have often been grouped with other types of drugs, such as antipsychotics or antidepressants, as well as nonbenzodiazepine antianxiety drugs. As noted above, many of the overdose cases involve ingestion of multiple substances. In the following sections, incidences of use of benzodiazepines in hospital surveys of drug overdose or coroners' reports have been determined by dividing the number of drug detections by the number of subjects in the survey, rather than by the incidence of drug detection. Thus, the rates given are not affected by the selection of drugs for which screening was attempted, nor by differences among drugs with respect to the sensitivity of the analytical techniques used. Where possible, the incidences of detection of benzodiazepines have been compared with those of barbiturates as a class; barbiturates were selected for this comparison because, during much of the period covered by the surveys reviewed, their availability and therapeutic indications were roughly similar to those of the benzodiazepines. It should also be kept in mind when interpreting these studies that the populations surveyed were not representative samples of the countries or regions in which these surveys were conducted.

a. HOSPITAL CASE SURVEYS. Drug overdose cases, as reported in the surveys reviewed here, must be regarded as somewhat selective. Clearly, many instances of over-

dose do not result in emergency room visits. For example, a study of telephone calls to a poison control center in the United States (971) found that 21% of calls referred to benzodiazepine ingestion, a considerably higher percentage than the incidence of benzodiazepine cases presented to emergency rooms in the country.

i. Presentations at emergency rooms. Table 30 shows the prevalence of presentations at emergency

TABLE 30

Hospital cases associated with benzodiazepine use: emergency room presentations; poison center admissions; and clinical toxicology laboratory samples

Study	Survey locale	Yr of survey	No.	% benzodiazepine	% barbiturate	% benzodiazepine mortality	% barbiturate mortality	Notes
Walberg et al., 1978 (1125)	U.S.A.	1972	9,985	0	43			All tests submitted to a clinical toxicology lab
		1976	14,239	1	22			
Horwitz et al., 1976 (491)	U.S.A.	1974–5	1,013	6	20			All tests submitted to a clinical toxicology lab
Teitlebaum et al., 1977 (1078)	U.S.A.	1975	260	7	6			Sample analyses submitted to a clinical toxicology lab
Baily and Guba, 1979 (31)	U.S.A.	1978	1,503	4	22			All tests submitted to a clinical toxicology lab
Baily, 1984 (30)	U.S.A.	1981–4	289	6	13			Emergency room ethanol-positive cases only
MacEachen et al., 1968 (691)	Canada	1959–65	24,242	3	7			All toxicities reported to the Canadian Poison Control Center
Ruedy, 1973 (946)	Canada	1972	349	24	10			
Sellers et al., 1981 (994)	Canada	1975	3,548	34	14	0	0	All toxic agents (substances other than drugs were about 2% of sample)
Qirbi and Poznanski, 1977 (897)	Canada	1977*	235	26	17			All tests submitted to a clinical toxicology lab
Busto et al., 1980 (148)	Canada	1980*	2,723	39				Overdose cases only
Rangno et al., 1982 (905)	Canada	1982*	304	50	18			
Lawson and Mitchell, 1972 (640)	Scotland	1960–5	361	3	50			All toxic agents, subjects' age 12 or older
		1966–71	580	15	20	0	3.9	
Proudfoot and Park, 1978 (896)	Scotland (Edinburgh)	1967	964	9'	30			Subjects' age 12 or older
		1976	2,134	40	15			
Matthew et al., 1969 (720)	Scotland (Edinburgh)	1968	1,067	12	26	0	0.6	All toxic agents
Haider et al., 1971 (419)	Scotland (Edinburgh)	1968–9	127	15	39	0	0	Drugs excluding CO
Matthew et al., 1972 (721)	Scotland (Edinburgh)	1968–70	1,189	9	59	0	1.6	Hypnotic drugs only
Prescott and Highley, 1985 (885)†	Scotland (Edinburgh)	1983	230	37				
Volans, 1981 (1123)	England	1977	1,252	4	3			Drug overdose. Tests submitted to a clinical toxicology lab
Jensen, 1974 (530)	Denmark	1950	100	0	75	0		All toxic agents
		1971	109	8	50	0	1.6	
		1973	101	13	33	0	1.7	

TABLE 30—*continued*

Study	Survey locale	Yr of survey	No.	% benzodiazepine	% barbiturate	% benzodiazepine mortality	% barbiturate mortality	Notes
Bjaeldager et al., 1984 (83)	Denmark	1980	1,330	27	?	0.2		All toxic agents. Mortality entry is frequency of sole benzodiazepine deaths
Cocchi and Invernizzi, 1968 (183)	Italy	1963–7	1,027	13	18			Suicides
Malizia et al., 1965 (699)	Italy	1964	72	7	39			Acute intoxications due to CNS depressants and antihistamines
Milla et al., 1977 (761)	Spain	1975–6	363	31	44			All toxic agents, subjects over 10 yr of age
Jacobsen et al., 1984 (518)	Norway	1980	1,192	18	7	0.1	0.7	All toxicities including those dying before reaching hospital
Freeman et al., 1970 (319)	Australia	1968–9	333	16	41			Drug overdose, subjects 12 yr or older
Ray et al., 1986 (908)	Australia	1982	158	49	51			Excludes ethanol-related cases
Babik and McLean, 1977 (96)	Australia	1974	187	43	32	0.5	0	
Ironside, 1969 (514)	New Zealand	1967–8	37	16	22			Suicide attempts
Sharman et al., 1972 (1007)	New Zealand	1971	1,181	12†	13†			All toxic agents
Large, 1978 (636)	New Zealand	1976–7	556	44	10			All toxic agents

* Date of publication; survey date(s) not provided.
† Estimate from graph.

rooms, admissions to specialized poisoning centers, surveys of drugs detected in samples submitted to clinical toxicology laboratories for analysis, and one study of calls to a poisoning control center. The incidence of benzodiazepine detection in surveys of emergency room cases ranged from zero to 50%. Ignoring the variations in methods across the different studies, the proportion of overdoses involving benzodiazepines appears to depend on geographical location. For example, the incidences of benzodiazepines in emergency room cases in the United States in surveys conducted in the mid-1970s were generally around 4 to 7%. In studies conducted in the mid-1970s to early 1980s in Canada, the incidences of benzodiazepines were generally higher, ranging from 24 to 50%.

Studies from the United Kingdom and Western Europe reported frequencies of detection of benzodiazepines, during the mid-1970s to 1980s, ranging from 4% in England (1123) to 40% in Scotland (896). Incidences ranging from 12% (1007) to 44% (636) were found in New Zealand and Australia from the late 1960s to the late 1970s (table 30).

Reports of the incidence of intake of various drugs in poisoning cases over several years have been provided by the Poison Control Center in Edinburgh (896, 720, 419, 721, 885, 884); these reports offer the advantages that they sampled cases from the same geographical area over a relatively long time period and employed generally comparable methods. These studies showed an increase in incidence of benzodiazepines over the period from 1967 to 1983, with a corresponding decrease in the incidence of barbiturate use, from 30 to 39% in the late 1960s to 15% in 1976 (table 30). The absolute numbers of patients ingesting benzodiazepines admitted to the Center increased from the mid-1960s to mid-1970s and thereafter declined somewhat. However, the proportion of all patients who had ingested benzodiazepines steadily increased over the years reported (1964 to 1979). A significant proportion (about 40%) of these patients had also ingested other drugs, and an unspecified but significant number had also taken alcohol (884). A similar increase in use of benzodiazepines and corresponding decrease in use of barbiturates were observed by Jensen (530) in Denmark in the years 1950, 1971, and 1973.

Busto et al. (148) found that the incidence of benzodiazepine intake in overdose cases, presumably suicide attempters, was lower than that for emergency room cases involving drug abusers.

The mortality rate of emergency room presentations was uniformly quite low in subjects for whom benzodiazepines were detected (table 30). Similarly, of over 8,000 patients treated for poisoning in Edinburgh, benzodiazepines were involved in only 7 deaths, in keeping with the low mortality rate in emergency room surveys. Only 2 of the deaths in Edinburgh followed ingestion solely of benzodiazepines; only one of these deaths could be attributed unequivocally to benzodiazepine poisoning (884). A similarly low incidence of lethality was found in surveys of coroners' reports, as discussed below.

The incidences of barbiturate detections in surveys of emergency room cases in the United States during the mid-1970s to 1980s ranged from 6% (1078) to 22% (1125) (table 30). Incidences within this relatively wide range were reported in Canada (946, 994, 905), Scotland (896), Denmark (530), Norway (518), Spain (761), Australia (96), and New Zealand (636). A relatively low incidence was reported by Volans (1123) in England.

In contrast to the findings regarding benzodiazepines, there was a general decline in incidence of detections of barbiturates over time. For example, Walberg et al. (1125) found a decrease from 43% to 22% from 1972 to 1976 in the United States. In studies from the Poison Control Center in Edinburgh, incidences of barbiturate detection ranged from 26% to 39% in the late 1960s to 15% in 1978 (896, 720, 419). In Denmark, Jensen (530) found decreases from 75% in 1950 to 50% and 33% in 1971 and 1973, respectively. As with the benzodiazepines, the incidence of detection of barbiturates in fatalities was low; however, the incidence was higher for barbiturates than it was for benzodiazepines.

ii. Hospital admissions. Patients subsequently admitted to hospitals following overdose are generally the more critical of the cases seen in the emergency room; surveys of these cases are shown in table 31. Surveys from the United States generally showed incidences of benzodiazepines ranging from zero (243, 687) to 15% (243). However, much higher incidences were found in one report (1057) of admissions to a military hospital.

Studies of hospital admissions in Canada (946), England (1077, 216, 796, 795), Scotland (1023), Italy (361), Australia (131, 800), and Singapore (166) uniformly reported incidences of benzodiazepine detections higher than those reported in the United States, ranging upwards from about 30% during the mid-1970s to early 1980s. Somewhat lower incidences were reported in England (729), Scotland (772), and New Zealand (1175) during earlier time periods.

An extensive survey of hospital admissions for drug overdose in the United States showed that 13% involved benzodiazepine ingestion (380). This rate of admissions is low relative to rates of benzodiazepine detection in surveys of samples submitted to clinical toxicology laboratories (table 30). Of all admissions involving benzodiazepines, in only 12 (1.6%) was a benzodiazepine the only agent ingested. These patients recovered without serious complications. The majority (87.9%) of benzodiazepine cases involved ingestion of multiple drugs. Indices of severity—such as the percentage of cases needing assisted ventilation or those at grade three or four of CNS depression—were low for cases of ingestion of benzodiazepines alone and for cases in which analgesics were ingested together with benzodiazepines. These indices were significantly increased when benzodiazepines had been taken with other drugs, such as barbiturates, other sedative-hypnotics, ethanol, other psychotropics, or miscellaneous drug combinations. Cases in which benzodiazepines and barbiturates had been combined did not appear to be more serious than cases of barbiturate overdose alone.

iii. Admissions to intensive care units. The most serious of overdose cases are admitted to intensive care units (ICUs). Surveys of these cases are shown in table 32. The incidence of benzodiazepines in these cases varied across studies, from 3% (782) to 38% (904). A comparable range of variation was seen in studies exclusively from the United States (526, 364, 1039). The incidence of detection of benzodiazepines in Finnish ICUs was about 20% in 1973, generally over 40% in 1974 through 1979, and declined to about 30% in 1980 through 1982 (25, 26). Overdose proved fatal in very few of these subjects. Benzodiazepines had been ingested by a very small proportion of those that died, and, as in the surveys described previously, these subjects had not necessarily ingested benzodiazepines alone.

With a few exceptions, in studies conducted until the mid-1970s, barbiturates were detected more frequently in ICU cases than were benzodiazepines. This contrasts with many of the results obtained in surveys of the less serious cases from emergency rooms and hospital admissions. In most ICU surveys from the late 1970s to early 1980s, however, this relationship was reversed.

As in the surveys described above, benzodiazepines were associated with very few deaths. Only one study reported deaths associated with benzodiazepine ingestion. The frequencies reported in these surveys were not different from the frequencies reported in the surveys of the less serious overdose cases. In contrast, barbiturates were associated with more deaths in these serious cases, and the frequencies were generally somewhat higher than those observed in surveys of the less serious cases.

b. CASE REPORTS. This section reviews a selection of illustrative case studies of benzodiazepine overdose. These studies provide an indication of the types of effects observed at high doses of benzodiazepines. While case reports can be informative, they can also be misleading; the fact that many published case reports represent exceptional rather than typical cases is sometimes overlooked. It should be recognized that case reports cannot substitute for controlled clinical studies.

Signs of benzodiazepine overdose observed in case studies vary with the particular drug, the doses involved, and the age of the patient. Generally, at relatively low

TABLE 31

Hospital admissions associated with benzodiazepine use

Study	Survey locale	Yr of survey	No.	% benzodiazepine	% barbiturate	% benzodiazepine mortality	% barbiturate mortality	Notes
Hauschild, 1968 (443)	U.S.A	1957–66	1,530	9	24			Suicide attempts with drugs
Greenblatt et al., 1977 (380)	U.S.A.	1962–75	773	13		0		
Whelton et al., 1973 (1134)	U.S.A.	1963–7	234	3	39	0	1.1	
		1968–70	285	4	30	0	2.4	
Dorman, 1979 (243)	U.S.A.	1968–70	32	0	10			
		1973–5	25	15	0			
Law et al., 1972 (638)	U.S.A.	1972*	84	8	41	0	1.4	
Lundberg et al., 1974 (687)	U.S.A.	1972	10,092	0	43			
Samuels et al., 1979 (968)	U.S.A.	1973–7	?	7	20			
Strong, 1984 (1057)	U.S.A.	1976–81	229	21	13			All toxic agents. Subjects over 13 yr old
Ruedy, 1973 (946)	Canada	1972	108	32	19			All toxic agents
Mawer et al., 1971 (729)	England	1963–7	415	3	64	0	1.7	Including CO
Vale, 1974 (1107)	England	1973	324	35	24	0	1.2	
Dallos, 1981 (216)	England	1977	204	36	12			
Helliwell et al., 1981 (451)	England	1978	108	50	47			Drug-induced comas originally referred due to unknown cause
Murphy et al., 1984 (796)	England	1980–2	1,055	50		0.2		
Murphy, 1982 (795)	England	1982*	83	45	5			Suicide attempts
Mitchell and Lawson, 1974 (772)	Scotland	1965–71	637	23	29			All toxic agents. Subjects over 12 yr old
Smith et al., 1983 (1023)	Scotland	1980–81	205	34	1	0.5		
Lamisse et al., 1973 (630)	France	1967–72	757	32	64			Cases of toxic coma in elderly
Bourim and Breteau, 1979 (124)	France	1979*	2,080	10				
Guinta et al., 1981 (361)	Italy	1978	436	27	2			All toxic agents
Bridges-Webb, 1973 (131)	Australia	1970–71	20	30				
Myers et al., 1981 (800)	Australia	1976–9	963	35	11	0	0.1	
Wright-St. Clair, 1975 (1175)	New Zealand	1963	190	1	15	?	?	All toxic agents
		1973	352	21	8	0	0	
Chee and Teo, 1984 (166)	Singapore	1982	80	29	6			
Bharja, 1970 (74)	Indonesia	1969–70	7	0	0	0	0	Suicide attempts

* Date of publication; survey date not provided.

doses, patients are somewhat somnolent and exhibit ataxia (1210, 177, 1086, 466, 45). At higher doses, patients are often comatose and areflexic; when awake these patients exhibit nystagmus, ataxia, dysarthria, and occasionally hypotension (1210, 420, 923, 332, 1212, 386). Both very young (63, 1029) and very old (492) subjects appear to show these signs at lower doses. These findings are in agreement with results of previously reported surveys of case studies (218, 738, 380).

A case of nonfatal cardiac arrest has been reported after diazepam overdose (70 mg) in a 2-yr-old child (63). Case reports of death following benzodiazepine ingestion are exceedingly rare (218); however, it has been reported after overdose with an undetermined amount of nitrazepam (362). Death has also been reported after an estimated 2.4 g of flurazepam; however, since the postmortem examination was conducted on this victim, found by a roadside, approximately 3 mo after death, it is unclear whether this was indeed a drug-induced death.

A few case studies have offered some suggestive evidence that the effects of high doses of lorazepam and triazolam may differ from those of other benzodiazepines. Overdose with lorazepam has resulted in hallucinations (335, 334, 527, 1119). Triazolam overdose has been reported to produce tremor, pupil dilation, and hyperreflexia (1088).

Case reports of multiple drug ingestion have indicated some effects that differ from those observed with overdoses of benzodiazepines alone. Respiratory depression appears to be an infrequent sign in cases of exclusive

TABLE 32

Intensive care unit admissions associated with benzodiazepine use

Reference	Survey locale	Yr of survey	No.	% benzodiazepine	% barbiturate	% benzodiazepine mortality	% barbiturate mortality	Notes
Jay et al., 1975 (526)	U.S.A.	1967–71	195	4	49	0	3.1	Sedative overdose only
Glauser and Smith, (not dated) (364)	U.S.A.	1971–4	162	17	69			
Stern et al., 1984 (1039)	U.S.A.	1977–81	283	32	13			
Rangno, 1975 (904)	Canada	1972–3	169	38	12			
Bismuth and Elkhouly, 1983 (77)	France	1979–80	1,000	21	12	0.1	0.2	
Frati et al., 1983 (316)	Spain	1974–80	82	18	62	0	2.2	
Arvela and Jounela, 1982 (25)	Finland	1979–81	475	23	8			
Morgan, 1975 (782)	Australia	1969–74	159	3	40			
Boxall and Chauvel, 1966 (127)	New Zealand	1963–4	100	7	68			All toxic agents

benzodiazepine overdosage, but has been reported with some frequency in cases of multiple drug ingestion (376, 973, 917, 616, 964). Additionally, death has been reported in cases where benzodiazepines had been combined with other drugs (288, 290, 1087, 366), but appears to be reported infrequently in cases of ingestion of benzodiazepines alone.

c. SURVEYS OF CORONERS' REPORTS. Reports of coroners often distinguish between drug-induced deaths and drug-related deaths. The former designation is applied when the coroner believes there is good evidence that the proximate cause of death was drug overdose. The latter designation is applied in cases where the drug may have contributed to the fatality only indirectly; for example, a drug-induced performance impairment may lead to a fatal accident. Also included in the "drug-related" category are deaths in which the victim had detectable tissue levels of drug, although death was not necessarily related to the drug effect, for example, if drug was detected in a victim killed in an accident caused by another. Additionally, drug-related deaths include cases in which the effect of the drug has subsided prior to the fatality, since levels of many drugs can be detected in body tissues long after drug effects have dissipated. Obviously, the distinction between drug-induced and drug-related deaths is a difficult one for the coroner to make. Information on levels of drugs in body tissues, which is rarely provided in surveys, would help clarify some cases. For example, in one study (51), diazepam was often detected in blood but most frequently at therapeutic levels; thus, these deaths are unlikely to have been drug induced.

In the surveys reviewed (table 33), there was a low incidence of deaths in association with benzodiazepine use, generally ranging from zero (877, 372) to 8% (823, 336). One exception is a study by Caplan et al. (155); in this study benzodiazepines were detected in 19% of the drug-induced deaths. This figure excluded cases of deaths associated with narcotics, which, if included, bring the incidence of benzodiazepines to 14% of cases. If cases involving carbon monoxide are also included, the incidence of deaths associated with benzodiazepines is further reduced to 8%. These figures are most consistent with those reported in the other studies shown in the table, which generally included deaths associated with narcotics and carbon monoxide.

In a study of deaths from poisoning in England and Wales, Osselton et al. (832) surveyed the incidence of all poisonings over the period from 1973 to 1980. During that time, the incidence of benzodiazepine detections increased from 5% in 1973 and 1974 to just over 9% in most years from 1977 to 1980. An exceptional year was 1979, during which benzodiazepines were detected in 15.6% of the victims. During the same time period the incidence of detection of barbiturates decreased from a high of 70.6% in 1974 to 32.3% in 1980. These trends are similar to those observed in the hospital surveys, as described above.

In those studies that reported the incidence of deaths due solely to benzodiazepines, the incidence was very low (236, 573, 877, 298, 336, 155); only three surveys of coroners' reports of drug-induced deaths found deaths due solely to benzodiazepines. Finkle et al. (299) reviewed the case files of 1,239 deaths in which diazepam was implicated; only 2 of these cases could be substantiated as resulting from diazepam alone. Similarly, case studies in which death resulted from exclusive benzodiazepine ingestion are rare (362). The low incidence of deaths associated with benzodiazepines in England and Wales was related by Barraclough (48) to prescriptions; the number of deaths per million prescriptions over the years 1965 to 1970 was 133 for barbiturates and 11 for nitrazepam.

d. THE DRUG ABUSE WARNING NETWORK (DAWN). The DAWN is a system funded by the National Institute on Drug Abuse in the U.S. for gathering information on drug involvement in emergency room presentations and

TABLE 33
Fatalities associated with benzodiazepine use

Reference	Survey locale	Yr of survey	No.	% benzodiazepine	% barbiturate	% solely benzodiazepine	Notes
Drug-related deaths							
Dinovo et al., 1976 (236)	U.S.A.	1972–74	2,609	4	33	0.13	Drugs only
Kelly et al., 1982 (573)	U.S.A.	1976–77	1,662	7	?	0	Drugs only
Blanke, 1974 (85)	U.S.A.	1970	132	2	37		Drugs only
Caplan et al., 1985 (155)	U.S.A.	1975–80	707	19	33	1.7	All toxic agents
Garriott et al., 1986 (337)	U.S.A.	1985	241	4	2		Drugs and homicides only
Drug-induced deaths							
Garriott et al., 1982 (336)	U.S.A.	1971–80	1,115	8	19	0.5	All toxic agents
Anonymous, 1972 (19)	U.S.A.	1972	92	1	25		Drugs only
Poklis and Ganther, 1981 (877)	U.S.A.	1977–79	61	0	25	0	Drugs only
Gupta and Kofoed, 1966 (412)	Canada	1955–64	2,018	0	26		All toxic agents
Vale, 1977 (1108)	England	1972–73	96	2	27		Drugs only
Osselton et al.							
1980 (833)	England	1973–75	23,174	8	54		All toxic agents
1984 (832)	Wales	1973–80					
Gormsen and Lund, 1982 (372)	Denmark	1974–75	677	0	47		All toxic agents

medical examiners' cases. Although the DAWN data are of the same types as those described above, this system is considered separately here because it represents some unique features; although it was not intended to provide information generalizable to the national population, the system has collected and reported information from numerous sites in the U.S. on a regular basis since 1972. Reports from participating emergency rooms and medical examiners in a number of metropolitan areas in the United States are tabulated in an effort to detect the emergence of novel drugs of misuse, as well as to determine the frequency of misuse of drugs in general. The DAWN reporters are trained in an effort to ensure concordance in definition and interpretation. Periodic reports present cumulative information regarding drugs implicated in the cases studied, whether used alone or in combination with other drugs, reported motivation for drug ingestion, demographic characteristics of the cases, medical disposition, etc.

There have been many changes, since the program began, in the metropolitan areas from which data are gathered, as well as in the reporting sites within these areas. (In 1985, DAWN data were reported from 27 metropolitan areas.) There have also been numerous changes in the system's methods of data collection.

Previous publications considering the reliability and validity of the DAWN system data, to which readers might wish to refer, include those by Swisher and Hu (1067) and Ungerleider et al. (1103, 1104).

The basic datum in a DAWN case report is a "mention" of a drug, which indicates that the drug was reported, or detected through toxicological analysis, to have been consumed by the subject. Although the periodic DAWN reports cumulate these mentions for individual drugs and drug groups, the incidence of mentions of any given drug should not be construed as a direct measure of its potential to produce toxic effects. First, in reports of emergency-room cases, a drug mention may reflect only the subject's self-report of drug use, or reports by other individuals associated with the subject, without laboratory confirmation of drug ingestion. In addition, a typical case involves mentions of multiple drugs; it is often unclear which of the drugs ingested, or which drug combinations, may have produced the toxic effects in question.

We examined DAWN data for the 5-yr period from 1981 through 1985 (804–808). In this period, the incidence of benzodiazepine mentions in emergency room cases decreased from 22.1% to 19.2%. The incidence of mentions of barbiturate sedatives also declined, from 7.7% to 4.2%. Deaths associated with either benzodiazepines or barbiturates in emergency rooms were extremely rare, with no change over this period.

The DAWN reports provide detailed information on several individual benzodiazepines, namely, those "commonly encountered brands" that are most frequently mentioned in the DAWN system; these also correspond to those most frequently prescribed, according to NPA data on prescription sales (505). In 1981 through 1985, these drugs included diazepam, chlordiazepoxide, clorazepate, lorazepam, and flurazepam. The incidence of emergency-room cases in 1981 in which one of these benzodiazepines was the only drug mentioned ranged from 0.4% to 3.6%, depending on the drug; except for

lorazepam, which remained relatively stable over this period, such exclusive mentions had declined by 1985 for each of these benzodiazepines, ranging from 0.3% to 2.2%. Likewise, cases in which a barbiturate alone was mentioned declined in this period from 1.9% to 0.8%. Thus, these drugs are rarely implicated alone in DAWN emergency-room cases.

The incidence of medical examiner cases in which benzodiazepines were mentioned in this period fluctuated between 14.8% and 18.1%, while that for barbiturates decreased from 23.9% to 12.0%. Over this 5-yr period, considering deaths listed as either drug induced or drug related, diazepam was the only drug implicated in about 1% of all cases. Sole mentions of flurazepam decreased from 0.5% to 0.1% over the period, while sole mentions of the other individually listed benzodiazepines fluctuated at very low levels (0.2% or less). By comparison, sole mentions of barbiturates decreased from 6.6% to 1.9% of all medical examiner cases.

Thus, benzodiazepines are implicated in about 20% of emergency-room cases, and in about 15% of medical examiner case reports, in the DAWN system. These are almost invariably cases in which other drugs are also implicated. These rates are higher than those found in most other U.S. surveys, but not higher than some similar surveys conducted in other countries (cf. tables 30 and 33 above); the higher rate from DAWN emergency-room cases may be due to the fact that these drug mentions did not require confirmation by toxicological analysis. In any case, these high incidence rates have often prompted concern about the abuse liability of the drug group and of individual benzodiazepines. Since these data thus appear at variance with other data bearing on the relative liability of these drugs for misuse (e.g., see sections IV C and V G 1 above), it seems appropriate to consider the context in which these DAWN figures might most reasonably be interpreted.

Baum et al. (56) suggested that the absolute numbers of DAWN mentions of each drug should be considered in relation to the extent of the drug's total use among the general population. They divided the number of DAWN mentions (projected to a national level for a number of drugs) by the total number of prescriptions sold for each of these drugs (according to NPA data). In this analysis, while diazepam ranked first among DAWN mentions in 1983, it ranked sixth when considered in relation to its total use.

A similar type of analysis was conducted by Jones (541), who divided DAWN mentions for November 1975 by amounts of drug prescribed, adjusted to compensate for potency differences among drugs. When this calculation was applied to 11 sedatives and hypnotics, diazepam, which ranked first among these drugs in DAWN mentions, dropped to eighth; similarly, chlordiazepoxide, flurazepam, and clorazepate, which ranked third, fifth, and eleventh in DAWN mentions of these sedative-hypnotics, changed in rank to eleventh, seventh, and tenth, respectively. In contrast, secobarbital, which ranked second in DAWN mentions among the sedative-hypnotics considered, ranked first when adjusted for amount and potency of drugs prescribed. This analysis indicated to the author that the abuse of diazepam relative to the amount prescribed is lower than that for secobarbital. Jones conducted a similar analysis of DAWN data on a group of ten drugs including minor tranquilizers (diazepam and meprobamate), stimulants, opioids, and barbiturates; diazepam, which had ranked first on the basis of percentage of total mentions, was ranked ninth (above only meprobamate) when the analysis was adjusted for amounts prescribed and for relative potencies. Since there was a high correlation between mentions in DAWN and total presciptions based on IMS America data, Jones suggested that mentions in DAWN are a reflection of prescribing practices.

DAWN emergency-room reports include classifications of each case according to the reported or presumed "reason for taking substance(s)." The options available are: psychic effects; dependence; suicide attempt or gesture; unknown; or other. The data deriving from these classifications are difficult to interpret, for various reasons. One is that a single motive is reported for drug ingestion in each case, despite the fact that most cases involve multiple drugs; thus, each substance that the subject has ingested, for whatever reasons, may be linked with the subject's motive for taking one substance. In addition, the definition provided for "psychic effects" refers to subjective effects often associated with reinforcing effects of drugs; since the definition used for "dependence" incorporates features of both physiological and psychological dependence, and since reinforcing effects are integral to psychological dependence, there appears to be considerable overlap between "psychic effects" and "dependence."

In any case, suicide attempts or gestures are specified as the motives in the majority of DAWN reports implicating benzodiazepines; while these incidents represent misuse of these drugs, they do not reflect on their potential for producing dependence nor on their reinforcing effects. With respect to the motives classification, the benzodiazepines are similar to other classes of psychotherapeutic drugs mentioned in DAWN reports, i.e., antidepressants and antipsychotics. This similarity draws attention to the fact that patients for whom these drugs are prescribed, who are relatively likely to have emotional problems, are also likely to be at increased risk for self-harm. It is also of interest that, with respect to the DAWN profile of motives for ingestion, the benzodiazepines are similar to these drug classes that are known to have no appreciable liability for abuse, whereas all of these psychotherapeutics differ in "motive profile" from illicit drugs, such as marijuana, stimulants, and hallucinogens, as well as certain narcotic analgesics.

These considerations emphasize the importance of characteristics of the populations using these different

types of drugs, as well as characteristics of the drugs themselves, as determinants of DAWN findings. It seems most reasonable to assume that a considerable variety of factors influences the selection of the populations represented in DAWN reports; these selection factors have not been explored in detail, rendering interpretation of the system's data extremely difficult at best. However, it seems clear that the simple frequency with which a drug is mentioned in DAWN reports is not intrinsically meaningful, and that listings of drugs according to these frequencies are likely to be misleading.

e. SUMMARY AND DISCUSSION. The incidence of detection of benzodiazepines in overdose surveys and in coroners' reports depends on geographical location, the period during which the survey was conducted, and the population studied. Over time, the incidence of benzodiazepines in these cases has generally increased, but appears to have stabilized in recent years. The signs observed after benzodiazepine overdose depend on dosage and specific drug, but generally included somnolence or coma, ataxia, dysarthria, and areflexia. There are few cases of lethality due to overdose with benzodiazepines alone.

In the context of the extent of use of benzodiazepines, as discussed previously in this review, the incidence of benzodiazepines in overdose surveys is not exceedingly high and may simply reflect the general availability of these drugs (1139, 2; but see also ref. 356). However, simple availability may determine accidental overdose to a greater extent than it determines intentional overdose.

Factors predisposing to prescription of a certain drug may also predispose to, or may be associated with factors that predispose to, intentional drug overdose. For example, in a prospective survey, Skegg et al. (1017) found the highest self-poisoning rate in subjects prescribed antidepressants, followed in order by those receiving prescriptions for minor tranquilizers, hypnotics, and major tranquilizers. Patients who seek help for psychiatric problems and who receive psychotropic drug prescriptions may be more likely to inflict self-harm than persons not receiving such prescriptions.

The benzodiazepines are associated with a very low risk of fatal overdose. Since overdoses involving benzodiazepines alone cause death only rarely (299), it seems appropriate further to ask to what degree do benzodiazepines contribute to death that ensues from multiple drug ingestion; that is, given a combination of a benzodiazepine with another compound, what is the nature of the interaction? Clinical studies cannot directly address this question; however, studies of 50% lethal dose (LD_{50}) values in animal subjects can provide some relevant quantitative information. Unfortunately, there is little such information available. The studies that are available concentrate on interactions of benzodiazepines with either opioids or ethanol. In one study (1110), the LD_{50} of ethanol was not appreciably altered by diazepam (15 mg/kg); however, the LD_{50} of diazepam was decreased by treatment with ethanol (800 mg/kg). In another study, 40 mg/kg of chlordiazepoxide did not alter the LD_{50} value of methadone (696). However, another study (1005) found that diazepam and oxazepam increased the LD_{50} values for methadone and morphine.

Studies employing more doses of benzodiazepines in combination with a range of doses of the other drug would allow an isobolographic analysis (675) that would shed light on the nature of the interaction of benzodiazepines with other drugs in overdose. In one study (277), results indicated that combinations of nitrazepam and ethanol were supraadditive. In another study (823), combinations of chlordiazepoxide and ethanol were infraadditive for lethality while supraadditive for loss of righting reflex. The LD_{50} value for chlordiazepoxide was not altered at all by ethanol doses up to 4.0 g/kg. These results suggest that the effects of combinations of ethanol with benzodiazepines may vary with specific benzodiazepines. The lethal effects of nitrazepam in combination with ethanol can be greater than the effects that would be predicted on the basis of an additive effect of the two drugs given alone; however, the lethal effects of chlordiazepoxide are not altered by concurrent administration of ethanol.

Finkle et al. (299) suggested that an indication of the safety of a drug is the frequency with which ingestion of that drug alone is responsible for overdose deaths. These investigators and others found a low incidence of deaths in overdose cases involving benzodiazepines alone, compared with cases in which benzodiazepines had been consumed together with other drugs. These conclusions are consistent with epidemiological evidence (48) that benzodiazepines are associated with few deaths per prescription, many times fewer than the number of deaths per prescription associated with barbiturate use. The low incidence of deaths associated with these drugs suggests that the benzodiazepines are among the safest of psychotherapeutic agents.

3. Mortality associated with benzodiazepine misuse or dependence. Piesiur-Strehlow et al. (870) cited a number of studies indicating that dependence on alcohol or on narcotics increases the risk of early death. These investigators examined mortality rates among patients who had abused, or had been dependent on, benzodiazepines alone or in combination with other drugs. The cases were 384 patients of a German university psychiatric hospital between 1975 and 1982, who fulfilled DSM-III criteria for dependence on substances similar to barbiturates. For each of 62 patients dependent on benzodiazepines alone, a control subject was selected from among other patients of the hospital. The controls were selected to match the dependent patients with regard to sex, age, and psychiatric (or other) illness. The psychiatric diagnoses for the dependent patients (other than the diagnosis of dependence itself) were chiefly of neuroses and affective disorders; for the few dependent patients with no other psychiatric diagnoses, age- and sex-matched

controls were selected from among patients with herniated lumbar disks. For both cases and controls, observed deaths (based on followup investigations) were compared with expected deaths for the average population (based on standard life tables); for each patient, the time between the date of first diagnosis and followup was considered as the time under risk.

Mortality rates were significantly increased in patients dependent on benzodiazepines in combination with alcohol (ratio of observed to expected deaths = 6.2) or with illegal drugs (ratio = 20.5). These rates of increased risk were in close agreement with those previously reported for subjects dependent on alcohol or illegal drugs. The mortality rate of patients dependent on benzodiazepines alone was also higher than that of the average population (ratio of observed to expected deaths = 3.0); however, the same rate was found among the group of matched controls. (Causes of death in the dependent group were one suicide, one cardiac infarction, and two carcinomas; causes of death in the control group were three suicides and one carcinoma.) The investigators concluded that this study found no evidence of increased mortality associated with dependence on benzodiazepines alone; rather, as they pointed out, these findings suggested that the increased mortality rates among patients dependent on benzodiazepines alone could be explained by the risk of early death known to be associated with psychiatric illnesses.

H. Summary and Discussion

Benzodiazepines account for about three-quarters of world sales of minor tranquilizers, but for only a minority of world sales of hypnotics and daytime sedatives; market shares held by individual benzodiazepines vary considerably across countries and change rapidly over time, particularly as new members of the class are introduced. In most countries, benzodiazepine sales markedly increased from the mid- or late 1960s to the early or mid-1970s, then slowed or levelled off; in at least some countries, sales declined in the late 1970s and resumed a slight increase in the early 1980s.

Surveys of physicians and of prescription records, which have been conducted chiefly in the U.S., indicate that half or more of prescriptions for benzodiazepine anxiolytics are written by primary care physicians. About half of all patients receiving these prescriptions have primary diagnoses of mental disorders, while diagnoses for the remainder pertain chiefly to circulatory, digestive, and musculoskeletal problems. Most prescriptions for benzodiazepine anxiolytics and hypnotics are repeats, reflecting continued treatment. Benzodiazepines are frequently prescribed concurrently with other psychoactive drugs. Elderly patients are likely to receive benzodiazepine prescriptions for longer periods of use than those prescribed for younger patients; however, at least in the U.S., these prescriptions for elderly patients are likely to specify lower daily doses than those prescribed for younger patients.

Interview surveys have found that actual use of anxiolytics is generally appropriate, in that users report high levels of emotional distress. Patients who receive prescriptions for benzodiazepine anxiolytics tend to take less of the medication than prescribed and to decrease their intake over time.

Cross-national interview data collected in 1981 indicated that, on average, 12.5% of the adult populations of several Western European countries and the U.S. reported that they had used a prescribed anxiolytic or sedative medication in the prior year; this was slightly lower than the average prevalence rate found 10 yr earlier. Use of these medications was generally most prevalent among people in late middle age or the elderly and was about twice as prevalent among women as among men in all age categories.

Although most users in most countries reported that they had used these medications for relatively short periods of time, an average of 19% of users reported having used them regularly for 12 mo or longer; in the U.S., 11% of those who had used prescription hypnotics in the prior year had used them for 12 mo or longer. Some clinical evidence suggests that the prevalence of long-term use that actually represents continuous administration may be substantially less than that suggested by these interview studies. Long-term use of benzodiazepines appears most likely to develop in older patients, who are also likely to have multiple somatic health problems, and in patients with recurrent psychiatric problems of long duration, for which they have previously used psychoactive medication.

Nonmedical use and recreational use of benzodiazepines among adults and youths in the general population are trivial in extent; those who engage in such misuse do so only on an infrequent, occasional basis. Studies among populations of drug abusers do find some recreational use of these drugs, though the available evidence indicates very little preference for benzodiazepines as a primary drug of abuse in these populations. These findings are consistent with evidence from experimental research, which has demonstrated some reinforcing effects of benzodiazepines among sedative abusers but not among normal, anxious, or insomniac subjects. There is some evidence that methadone patients show a preference for benzodiazepines, and particularly diazepam, as an adjunct to methadone use; this possible preference merits further study.

Benzodiazepines are found with some frequency in surveys of overdose, usually in combination with other drugs. The incidence of benzodiazepine detection in these surveys is not disproportionate to the overall availability and medical use of these agents; this incidence may reflect the psychiatric illnesses for which these drugs are prescribed, which are associated with increased risk of self-harm. Overdoses in which benzodiazepines are im-

plicated rarely result in fatalities, and overdoses with benzodiazepines alone are almost never fatal.

VI. General Summary and Discussion

This review has examined the evidence regarding the abuse liability of the benzodiazepines. We have defined the abuse liability of a compound as its capacity to produce persistent self-administration (psychological dependence), or physiological dependence, in conjunction with the capacity to alter behavior in a manner that is detrimental to the individual or his social environment. In addition to the evidence on these matters, we have reviewed research on the extent and appropriateness of actual use of these drugs and on their involvement in misuse, recreational use, and overdose; we believe that this epidemiological information provides a perspective necessary to qualify the nature and overall significance of the abuse liability of drugs.

The ability of a drug to reinforce drug-taking behavior is an essential determinant of its liability for abuse. Only a few studies of self-administration in animals have indicated that benzodiazepines have robust reinforcing effects, and such effects have been reliably demonstrated only with the short-acting compounds. In the few studies of benzodiazepine self-administration that have been conducted in humans, a striking finding is the absence of reinforcing effect in normal subjects or in subject groups representing the populations for which benzodiazepines are most frequently prescribed. Self-administration studies in subjects with histories of sedative abuse have also shown virtually no reinforcing effects of doses within the therapeutic range, but modest reinforcing effects of higher doses. Some studies, particularly in sedative abusers, have found differences among individual benzodiazepines with respect to subjective effects or to preference for one compound over another; to date these remain intriguing but preliminary findings that may represent important differences among these compounds if they prove to be reliable and generalizable to other experimental conditions and other subject populations.

All benzodiazepines that have been tested appear capable of producing physiological dependence in various animal species. The qualitative characteristics of this dependence appear to overlap substantially, though not completely, with characteristics of barbiturate dependence. In humans, withdrawal signs have been clearly demonstrated following chronic administration of high doses; more recent studies have also demonstrated the development of a mild degree of physiological dependence in many patients receiving therapeutic doses for prolonged periods. There has been some suggestion that patients with histories of prior use of alcohol or other CNS depressants may be at increased risk of developing dependence on benzodiazepines; further study is needed to evaluate this possibility, and to clarify what extent of prior exposure to such substances, in terms of both dosage and duration, might be necessary to increase this risk. Some studies have suggested that the withdrawal syndromes associated with chronic administration of benzodiazepines may vary in accord with the half-lives of the individual compounds; however, the available evidence on possible differences among the benzodiazepines with respect to their capacities to produce physiological dependence is inconclusive. Although rigorous measures have not been applied, studies demonstrating physiological dependence to benzodiazepines have found no evidence that this dependence is associated with tendencies to increase dosage or other risks of inappropriate use.

Although their findings are not entirely consistent, laboratory studies of the effects of benzodiazepines on various types of human psychomotor performance have tended to show that acute administration of therapeutic doses of benzodiazepines can produce significant performance decrements in normal subjects, as well as in anxious and insomniac subjects; these decrements are substantially reduced following repeated administration of the drugs. Although well over 500 studies have been conducted, these studies considered together have not differentiated the types of performances most likely to be affected by the benzodiazepines as a group, nor have they demonstrated consistent differences among benzodiazepines with respect to these behavioral effects. It is not clear whether or how these laboratory findings of performance decrement may relate to effects of benzodiazepines on the routine behavior of patients using these drugs. Laboratory studies of real or simulated driving have suggested that benzodiazepines may alter driving behavior; however, epidemiological studies have not provided compelling evidence regarding the possibility that benzodiazepine use may increase the risk of automobile or other accidents. There is consistent evidence, particularly from studies measuring delayed recall, that benzodiazepines can produce impairments in recall; there is some suggestion that tolerance may not develop to these amnestic effects. Elderly patients are especially susceptible to the behavioral effects of benzodiazepines. Finally, studies of patients for whom benzodiazepines have been prescribed have found no effects of use of these drugs on subjective well-being, on interpersonal relations, or on work performance.

Surveys of physicians and of prescription records indicate that half or more of prescriptions for benzodiazepine anxiolytics are written by primary care physicians. About half of all patients receiving these drugs have primary diagnoses of mental disorders, while diagnoses for the remainder pertain chiefly to circulatory, digestive, and musculoskeletal problems. Interview surveys have found that actual use of anxiolytics is generally appropriate, in that users report high levels of emotional distress. Patients who receive prescriptions for benzodiazepine anxiolytics tend to take less of the medication than prescribed and to decrease their intake over time. Among the countries that have been studied in cross-

national surveys (several Western European countries and the U.S.), between 7 and 18%, or an average of 12.5%, of the adult populations use a prescribed anxiolytic in the course of a year; on average, 2% of the population takes an anxiolytic on any given day. Use is most prevalent among those in their 50s and 60s and is about twice as common among women as among men.

Although most users in most countries surveyed use these drugs for relatively short periods of time, an average of 19% of users report having used them regularly for 12 mo or longer. Prescription hypnotics are also used regularly for long periods by a substantial proportion of the population; e.g., 11% of users in the U.S. report regular use of hypnotics for 12 mo or longer. Long-term use of benzodiazepines appears most likely to develop in older patients, who are also likely to have multiple somatic health problems, and in patients with recurrent psychiatric problems of long duration, for which they have previously used psychoactive medication.

Despite the wide availability and extensive medical use of benzodiazepines, there are very little misuse or recreational use of the drugs among adults or youths in the general population and little preference for them among populations of drug abusers; these findings parallel those of the experimental studies of self-administration. Benzodiazepines are found with some frequency in overdose surveys, usually in combination with other drugs; this frequency is not disproportionate to the overall availability and medical use of these drugs. They are rarely implicated in fatal overdoses. Data from these surveys indicate that overdoses involving benzodiazepines are most likely to result from suicide attempts or gestures; these overdoses may therefore reflect a tendency to self-harm associated with the psychiatric conditions for which benzodiazepines are prescribed, rather than accidental consequences of recreational use.

In summary, although some studies have suggested differences among the benzodiazepines with respect to various measures related to abuse liability, the scientific evidence to date remains inconclusive and subject to further evaluation. On the whole, the benzodiazepines as a class of drugs are more similar than dissimilar, and they are significantly different from other compounds available for the same medical uses. Thus, at the present time, it seems most prudent to consider the available evidence regarding the abuse liability of benzodiazepines as relevant to the class in general. With respect to the abuse liability of the class, then, this review has found that the benzodiazepines are capable of producing physiological dependence; however, this physiological dependence is not usually accompanied by reinforcing effects (psychological dependence). In addition, benzodiazepines can produce decrements in recall and in psychomotor performance; the effects on psychomotor performance (but not necessarily the effects on recall) subside with repeated administration.

A. Implications with Respect to Abuse Liability

Thus, the benzodiazepines have limited liability for abuse, according to traditional criteria and relative to drug classes associated with significant potential and actual abuse. In addition, there are a number of indications that the profile of the effects of benzodiazepines relevant to abuse liability is qualitatively different from that of traditional drugs of abuse, as derived from assessment of opioids, stimulants, and barbiturates. That is, benzodiazepines have no reinforcing effects in normal subjects and are associated with little misuse or recreational use in the general population and little preference among populations of drug abusers. Also, in marked contrast to drugs with significant abuse, the frequency with which benzodiazepines are implicated in overdose cases is not disproportionate to their availability, they are rarely implicated in fatal overdoses, and overdoses in which benzodiazepines are involved usually result from suicide attempts or gestures, rather than from recreational use.

On the other hand, while benzodiazepines are of little concern with respect to the populations traditionally at risk of drug abuse, the large population for whom benzodiazepines are prescribed includes a substantial proportion of long-term users, many or most of whom are likely to have developed physiological dependence on these drugs. The risks associated with this dependence may be the most appropriate focus of concern with respect to the abuse liability of the benzodiazepines and with respect to the public health and social significance of this liability.

These considerations argue for a flexible approach to the concept of abuse liability in general. As in the instance of the benzodiazepines, there may be qualitative as well as quantitative differences among drugs or drug classes with respect to their relative liabilities for abuse, e.g., regarding the populations at risk, the predominant forms of abuse, and the nature and potential consequences of the risks of abuse. Such qualitative differences can have important implications for research strategies, for clinical practice, and for public policy approaches to dealing with the abuse liability associated with specific drug classes.

B. Research Implications

The most general implication of these findings for research is the need to redirect emphases with respect to the populations studied. The population of chief concern with respect to risks that may be associated with benzodiazepines is that of patients who receive prescriptions for these drugs for therapeutic uses, and particularly those who develop patterns of long-term use.

Experimental assessment of reinforcing effects of benzodiazepines should be undertaken in patients with diagnoses for which benzodiazepines are indicated, e.g.,

patients with a diagnosis of generalized anxiety disorder. We know virtually nothing about the determinants of drug taking in these populations. Are the reinforcing effects of benzodiazepines in these individuals different from those in normal subjects? Are there subgroups of patients who receive prescriptions for benzodiazepines that can be differentiated by measures that would predict which will become long-term users? How much do other factors, e.g., compliance or therapeutic effects, contribute to continued drug-taking? A variety of measures should be tested in such patient populations, alone and in various combinations; these measures should include those that have been used to evaluate effects in normal subjects and sedative abusers (e.g., ARCI subscales, POMS, etc.), and standard psychiatric rating scales, to explore possible relationships between therapeutic and reinforcing effects. These kinds of experiments should include assessments of the effects of acute doses in patients who are chronic users of these medications, as well as in patients beginning courses of anxiolytic or hypnotic medication.

Some studies have suggested various factors that may predispose to the development of physiological dependence to benzodiazepines; further study is warranted, especially to explore the possibility that prior use of depressants, e.g., alcohol, may increase this risk. Studies should also be undertaken to explore the possibility that elderly patients may be at increased risk of physiological dependence to benzodiazepines. Are elderly patients taking benzodiazepine hypnotics more susceptible than younger patients to rebound insomnia? Can physiological dependence be demonstrated at earlier points in treatment of elderly versus younger patients?

Studies of the effects of benzodiazepines on human psychomotor performance have not yielded results that are generalizable to situations outside of the laboratory. Unless it proves possible to develop behavioral tests with greater predictive reliability, it may be more fruitful to take a direct approach to measuring routine behaviors of representatives of the patient populations most likely to receive prescriptions for benzodiazepine medications. Although findings regarding the effects of benzodiazepines on recall have been more consistent than those regarding effects on other performances, further research is needed to determine whether these effects are sustained with chronic administration.

An extremely important area for epidemiological research is the investigation of the natural history of long-term use of benzodiazepines: its determinants; its development; characteristics of long-term users; actual patterns of long-term use, including concurrent use of other psychoactive substances; and the risks and sequelae of long-term use. Cross-sectional surveys can certainly be important sources of some of this information, particularly if they attempt to obtain careful histories from patients who have been long-term users. However, the most promising approach to this investigation is probably that of prospective, longitudinal studies, in which patients are followed from the time that they first receive prescriptions for benzodiazepine anxiolytics or hypnotics; although a number of investigators have commented on the difficulty of finding many such patients, the approach does appear feasible.

Epidemiological research is also needed to provide information, in terms of a wide array of public health parameters, on the abuse of individual benzodiazepines as it occurs in various geographical areas. It is equally necessary to determine appropriate means of evaluating information of this kind in the context of the availability and legitimate use of the individual drugs considered. These data could then be related to laboratory research on abuse liability of the compounds, so that laboratory and epidemiological research on drug abuse might be mutually validated.

Clinical studies are clearly needed on the benefits and risks of long-term use of benzodiazepines. In addition to standard psychiatric rating scales, these studies should also incorporate various measures of subjective effects and of social effects. Such studies might help to elucidate why so many patients who receive benzodiazepines continue to take them for long periods. Does long-term use reflect some sustained benefits of these drugs, or does it represent some form of inappropriate use linked with dependence? It has been suggested that benzodiazepine therapy should be interrupted periodically, both to assess whether patients need to continue medication and to reduce the risk of dependence development; however, the effects of such "drug holidays," both on therapeutic response and on the risk of physiological dependence, should be specifically evaluated.

C. Clinical Implications

Physicians should be aware that a mild degree of physiological dependence is likely to develop in some patients taking benzodiazepines on a regular basis for periods of several months. Even when physiological dependence does develop, however, the great majority of patients do not tend to increase their dosage, to use these drugs for recreational purposes, or to engage in other forms of inappropriate use.

In the absence of such risks of inappropriate use, the significance of physiological dependence in patients receiving benzodiazepine medication must be weighed against therapeutic benefits on a case-by-case basis. Since the risk of physiological dependence may increase with the duration of regular use, such benefit/risk judgments should be made through regular followup consultations in the course of treatment.

In patients receiving benzodiazepine hypnotics, rebound insomnia or early-morning awakening may occur as early symptoms of withdrawal. These symptoms may be less likely to develop with the use of compounds with

long half-lives; however, use of these compounds may also be associated with residual daytime sedation.

If patients who have developed physiological dependence stop taking benzodiazepines abruptly, they may experience increased anxiety and/or other symptoms of withdrawal; these symptoms may be uncomfortable, but are usually not of severe degree nor associated with serious medical or psychiatric sequelae. On the other hand, physicians can manage discontinuation of benzodiazepine treatment with minimal discomfort in dependent patients by prescribing a regimen of very gradual reductions in dosage.

Prior or concomitant use of other CNS depressants, including alcohol, may increase the risk that physiological dependence to benzodiazepines will develop, and concomitant use of such agents may substantially increase the risk of adverse behavioral effects or other toxic effects associated with benzodiazepine use.

At present there is no definitive evidence of differences among the benzodiazepines with respect to their relative liabilities to produce dependence. Therefore, selection of a specific benzodiazepine agent should be based on therapeutic criteria, rather than on speculation that one agent might be less likely than another to produce dependence.

Acute administration of benzodiazepines may be associated with certain decrements in performance; these decrements are diminished after several days of chronic administration. Physicians should admonish patients accordingly, especially if they are receiving benzodiazepines for the first time, are resuming use after an interval without this medication, or if they use these drugs on an infrequent, occasional basis.

Elderly patients may be more susceptible than younger patients to the behavioral effects of benzodiazepines. Thus, physicians are well advised, in general, to prescribe lower doses for elderly patients.

D. Policy Implications

Psychiatric epidemiology indicates that about 15 to 20% of every population studied is afflicted by psychiatric illness. The epidemiology of drug use indicates that sedative medications account for a significant proportion of all prescriptions, and that this proportion has not changed substantially, at least in several decades.

Benzodiazepines are less toxic, e.g., in cases of overdose, than other classes of drugs that have been used as anxiolytics, sedatives, or hypnotics, and they are among the safest of the psychotherapeutic medications currently available. They bear little liability for abuse among populations of drug abusers, and virtually none among the general population or typical patient populations. Nevertheless, a substantial proportion of the population uses benzodiazepines on a regular, long-term basis; very little is known about the determinants and risks of such use.

Regulatory intervention should be designed to address the specific types of risks associated with this class of drugs. In this connection, the regulatory controls now in effect in the U.S. appear appropriate.

A high priority should be accorded to research focused on patients representative of those who receive prescriptions for these drugs, and particularly on long-term users, rather than on drug abusers.

It should also be considered of great importance to educate physicians, especially including primary care practitioners, in practical methods for assessing the benefits and risks of initiating and maintaining benzodiazepine treatment on a case-by-case basis.

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VII. Appendix

References for table 2. The following refers to studies in which dose comparisons were conducted, as summarized in table 2. Studies in which a significant effect was observed are listed with an asterisk (*). Studies including multiple-dose comparisons are listed once per each comparison.

Drug	Test	Route	References
Alprazolam	CFF	p.o.	24, 1060*
Alprazolam	DSST	p.o.	24,* 612
Alprazolam	TRAC	p.o.	24,* 1060
Alprazolam	RT	p.o.	612
Alprazolam	CRT	p.o.	24, 1060
Alprazolam	CANC	p.o.	612
Chlordiazepoxide	CFF	p.o.	952, 470,* 360
Chlordiazepoxide	DSST	p.o., h.s.†	80*
Chlordiazepoxide	TRAC	p.o.	952, 1165, 655, 118, 655, 360
Chlordiazepoxide	RT	p.o.	118,* 360

VII. Appendix

Drug	Test	Route	References
Chlordiazepoxide	CRT	p.o.	952, 470,* 655,* 578,* 655*
Chlordiazepoxide	ARITH	p.o.	80*
Clorazepate	CFF	p.o.	620, 620, 620,* 620, 620*
Clorazepate	TAPP	p.o.	620, 620,* 620, 620,* 620
Clorazepate	DSST	p.o.	620, 620,* 620, 620,* 620
Clorazepate	RT	p.o.	620, 620, 620, 1035
Clorazepate	CRT	p.o.	1035
Clorazepate	CANC	p.o.	620, 620, 620
Clorazepate	ARITH	p.o.	1035
Diazepam	CFF	p.o.	407,* 448,* 819, 377,* 470,* 24, 487,* 997,* 788,* 712,* 1000,* 727,* 842,* 787,* 645, 418,* 71,* 726,* 437, 407,* 61,* 724,* 418,* 407*
Diazepam	CFF	i.v.	404,* 595,* 600, 600,* 600,* 599,* 317*
Diazepam	TAPP	p.o.	353, 354,* 428, 435, 1101,* 428, 435, 70, 369,* 1101,* 115, 369, 1101*
Diazepam	TAPP	i.v.	354,* 597,* 355,* 355*
Diazepam	DSST	p.o.	428, 428, 1166, 213, 369, 24,* 517,* 213,* 725,* 517,* 115,* 369,* 517,* 724,* 213*
Diazepam	DSST	i.v.	272,* 272,* 272,* 192*
Diazepam	TRAC	p.o.	273, 272,* 273,* 272,* 273,* 272,* 843, 655, 819,* 24, 843, 830, 725, 655, 174,* 173,* 1000,* 727, 842, 787, 645, 418, 118,* 437, 726, 843, 830,* 724, 418*
Diazepam	TRAC	i.v.	595,* 600,* 600,* 599,* 602, 600,* 328*
Diazepam	TRAC	p.o., h.s.	174, 174, 654, 173, 120*
Diazepam	RT	p.o.	353, 435, 1101, 1074,* 448, 819,* 27, 435, 70, 27, 1101,* 788, 430,* 118,* 115,* 375, 1101*
Diazepam	RT	i.v.	328,* 137,* 458,* 355, 275,* 355
Diazepam	CRT	p.o.	353, 843, 999,* 843,* 655, 470, 24, 997,* 843,* 788,* 655,* 174,* 727,* 842, 645,* 726,* 61,* 843,* 350
Diazepam	CRT	i.v.	595,* 600,* 600, 599, 602, 600,* 355
Diazepam	CANC	p.o.	354,* 435, 543,* 1046,* 435, 997, 788,* 725, 787,* 418, 724,* 418*
Diazepam	CANC	i.v.	354,* 238,* 597*
Diazepam	ARITH	p.o.	353, 354,* 543, 448, 1166
Diazepam	ARITH	i.v.	595,* 351,* 354,* 328,* 458*
Diazepam	SORT	p.o.	787, 418, 418
Diazepam	DV ATT	p.o.	843, 952, 843,* 665, 843,* 665, 655, 1000, 726, 843*
Diazepam	DV ATT	i.v.	595, 600, 600, 599,* 600
Flunitrazepam	TAPP	p.o., h.s.	114*
Flunitrazepam	DSST	p.o., h.s.	121, 121,* 121,* 114
Flunitrazepam	TRAC	p.o., h.s.	812, 121, 812, 121, 121*
Flunitrazepam	TRAC	p.o.	812*
Flunitrazepam	RT	p.o., h.s.	114
Flunitrazepam	CANC	p.o., h.s.	114
Flunitrazepam	SORT	p.o., h.s.	114
Flurazepam	CFF	p.o.	406*
Flurazepam	TAPP	p.o., h.s.	113, 113, 122
Flurazepam	DSST	p.o.	940,* 941,* 940,* 941*
Flurazepam	DSST	p.o., h.s.	940, 941, 113,* 1112, 940,* 941,* 113,* 80, 122
Flurazepam	TRAC	p.o.	940,* 940*
Flurazepam	TRAC	p.o., h.s.	940,* 952,* 940,* 874, 119,* 80

VII. Appendix—*continued*

Drug	Test	Route	References
Flurazepam	RT	p.o.	406
Flurazepam	RT	p.o., h.s.	113, 874, 113
Flurazepam	CRT	p.o.	941, 941
Flurazepam	CRT	p.o., h.s.	941, 113,* 941, 113,* 952, 122
Flurazepam	CANC	p.o.	406
Flurazepam	CANC	p.o., h.s.	113, 1140, 113
Flurazepam	ARITH	p.o.	941,* 941*
Flurazepam	ARITH	p.o., h.s.	940,* 940,* 941,* 80
Flurazepam	SORT	p.o.	940,* 940*
Flurazepam	SORT	p.o., h.s.	113, 1112,* 113, 940*
Flurazepam	DV ATT	p.o.	789,* 789*
Lorazepam	CFF	p.o.	448, 1092, 448,* 1092,* 61, 448,* 1092,* 448,* 1092,* 819,* 61,* 1060,* 997,* 995,* 293
Lorazepam	DSST	p.o.	292,* 295, 612,* 292,* 293,* 295,* 294*
Lorazepam	TRAC	p.o.	1092, 60, 1092,* 819,* 60,* 1060,* 997,* 995,* 723*
Lorazepam	RT	p.o.	448, 1092, 292, 448, 1092, 61,* 295,* 448,* 1092,* 819,* 34,* 612, 292,* 295*
Lorazepam	CRT	p.o.	1060,* 997,* 995,* 240
Lorazepam	CANC	p.o.	292,* 612,* 292,* 293,* 997*
Lorazepam	ARITH	p.o.	448, 448
Nitrazepam	CFF	p.o.	407,* 407,* 648
Nitrazepam	CFF	p.o., h.s.	476, 476, 467, 470, 389,* 722,* 952
Nitrazepam	TAPP	p.o., h.s.	853, 1127, 853, 623, 112, 1127, 853,* 623,* 112*
Nitrazepam	DSST	p.o.	853, 853, 700,* 701, 815, 853,* 700,* 701,* 815
Nitrazepam	DSST	p.o., h.s.	1013, 1127, 623, 112,* 1127,* 623,* 112,* 722
Nitrazepam	TRAC	p.o.	648*
Nitrazepam	TRAC	p.o., h.s.	119,* 722
Nitrazepam	RT	p.o.	1013, 214,* 214*
Nitrazepam	RT	p.o., h.s.	853, 1013, 1127, 623, 625, 431, 853,* 1127, 119,* 623,* 625, 431, 853*
Nitrazepam	CRT	p.o.	648*
Nitrazepam	CRT	p.o., h.s.	476, 654,* 467, 472, 470,* 469, 952, 476, 952, 654,* 722
Nitrazepam	CANC	p.o., h.s.	1140, 112,* 112*
Nitrazepam	ARITH	p.o., h.s.	112, 112
Nitrazepam	SORT	p.o.	700,* 701,* 700,* 701*
Nitrazepam	SORT	p.o., h.s.	112,* 703, 112,* 703*
Oxazepam	CFF	p.o.	779, 841,* 779,* 957,* 779*
Oxazepam	TRACT	p.o.	840,* 1055,* 1056,* 174*
Oxazepam	TRAC	p.o., h.s.	174, 174, 174*
Oxazepam	RT	p.o.	430, 331, 957, 1034*
Oxazepam	RT	p.o., h.s.	990
Oxazepam	CRT	p.o.	331, 841, 174
Oxazepam	DV ATT	p.o.	1068, 840
Oxazepam	DV ATT	p.o., h.s.	990
Oxazepam	ATT	p.o., h.s.	990, 957
Temazepam	CFF	p.o., h.s.	468, 648, 467, 468, 389, 722,* 467, 648, 468,* 467*
Temazepam	DSST	p.o.	876,* 612*
Temazepam	DSST	p.o., h.s.	941,* 722, 941*
Temazepam	TRAC	p.o.	174, 648, 174,* 876,* 648*
Temazepam	TRAC	p.o., h.s.	174, 648, 722, 174, 174, 874
Temazepam	RT	p.o.	612
Temazepam	RT	p.o., h.s.	941, 434, 874, 434, 941
Temazepam	CRT	p.o.	174, 648, 174,* 172,* 648

VII. Appendix—*continued*

Drug	Test	Route	References
Temazepam	CRT	p.o., h.s.	468, 174, 467, 389, 468, 174,* 467, 722, 468,* 467*
Temazepam	CANC	p.o.	876, 612*
Temazepam	CANC	p.o., h.s.	434, 434
Temazepam	ARITH	p.o., h.s.	941, 941*
Temazepam	SORT	p.o., h.s.	478, 478
Triazolam	CFF	p.o.	473
Triazolam	CFF	p.o., h.s.	301
Triazolam	DSST	p.o.	121, 121, 33,* 121, 611, 612*
Triazolam	DSST	p.o., h.s.	940,* 464, 1112,* 940,* 371, 1112*
Triazolam	TRAC	p.o.	940, 812, 464, 940, 812*
Triazolam	TRAC	p.o., h.s.	812
Triazolam	RT	p.o.	612*
Triazolam	CRT	p.o.	464
Triazolam	CANC	p.o.	33, 612*
Triazolam	CANC	p.o., h.s.	728, 728
Triazolam	SORT	p.o.	940,* 33,* 940*
Triazolam	SORT	p.o., h.s.	1112*

† h.s., administered at bedtime.

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