THE WIDESPREAD USE of tranquillizers in a society where the use of alcohol is even more widespread makes it important at this time to evaluate the effects of combining the two drugs. Several years ago one source (Hilgard) pointed out that six billion tranquillizers were consumed in one year in the United States. In addition, at least one group of investigators (Zirkle et al.) have shown in the laboratory that surprising and severe effects occur when therapeutic doses of a tranquillizer (meprobamate) are mixed with relatively small amounts of alcohol (0.05% blood alcohol level). The problem of combining these drugs when driving a car is complicated by the fact that people are not able to evaluate accurately their own condition, as far as we know. The caution of the social drinker when driving, if it exists, may be a function of the number of drinks he has had rather than his degree of intoxication.

The basic problem of driving studies is validity: that is, whether any test situation can adequately evaluate performance in an actual “free driving” situation. There is the problem of knowing what to measure and how to measure it; the technical difficulties in this area are often formidable. A third problem concerns differences in motivation in a testing situation as compared to actual driving; motivational and attentional changes due to the action of drugs are also a complicating factor.

Studies of the effect of tranquillizers on driving performances have used driving simulators. The subject operates a set of the same controls that are found in a car while he looks at a changing road scene projected in front of him. Measures of his position on the road, speed, braking time are obtained. The limitations of this apparatus have been discussed by various investigators, and workers studying the effects of alcohol have introduced various improvements in the test and have used driving courses. These investigators have been concerned with understanding both driving itself as a skill and its measurement. All but one of the studies of tranquillizers, however, have so far employed only the American Automobile Association (AAA) simulator, which is probably the least adequate simulator in use.

Actually there are so few studies of driving involving the use of tranquillizers, either alone or with alcohol, that there are not sufficient data on which to make any specific recommendations about driving. As long as some studies have shown that driving may be impaired with tranquillizers, the conservative position would advise using them with great caution when a car is operated.

If we turn to the experiments themselves, deterioration on driving tests due to alcohol has been shown to occur at low blood alcohol levels, 0.05%, by almost every investigator who has studied it (Carpenter). A comparable statement cannot be made for tranquillizers. The study of tranquillizers and driving has been limited, and is...
exceedingly complex in that tranquillizers are not a single pharmacological agent. Various tranquillizers have quite different chemical structures; they may have different sites of action in the brain, and they may be expected to have different effects on various behaviours.

Relatively mild effects or none have been reported after acute administration of various tranquillizers. The language of many of the reports makes it difficult to be exact about drawing conclusions. One is often left with the feeling that results are equivocal or borderline at best. A survey of the effects of eight tranquillizers on driving is presented in Uhr and Miller’s book, *Drugs and Behaviour* (Chapters 20, 21 and 22). Most other studies have been concerned with meprobamate. With respect to meprobamate and emylcamate, Uhr and Miller report that, “the 800 mg. dose of both drugs appeared to have some effect on components of psychomotor behaviour related to driving: emylcamate chiefly on reaction time, meprobamate a less specific effect on reactions and accuracy” (p. 203). They state further that, “no behavioural toxicity has been found by our tests for dosages of meprobamate of less than 800 mg., 400 mg. being the usual clinical dose.” In contradiction to this, Marquis found no impairment even after the higher dose, 800 mg. of meprobamate. Kristofferson and Cormack saw no deterioration after 800 mg. of oxanime (in Uhr and Miller, *Drugs and Behaviour*).

Loomis and West followed performance of subjects over a six-hour period and did find “Meprobamate [only 400 mg.] impaired performance two hours after the first dose and one hour after the second,” and there was mild deterioration due to chlorpromazine after four hours. It is difficult to determine from Marquis’ paper the length of his observation period. Since, for some subjects, the driving test was given first in the battery, they took the test 30 minutes after drug administration, and, according to the results of Loomis and West, they anticipated the critical time for meprobamate by 90 minutes.

Experiments with chronic administration of the drugs have not turned up more definite results. Zirkle and co-workers criticized the use of an acute dose of meprobamate as being unlike common clinical use of the drug, which is chronic. They found significant effects of meprobamate (1,600 mg. per day) and chlorpromazine (200 mg. per day) given for one week. Uhr (Uhr, Pollard and Miller), using anxiety neurotics as subjects, found some slowing of reaction time with meprobamate when 1,600 mg. per day was given for three weeks. Kelly, however, using 1,600 mg. per day for two to three weeks, found no impairment. Kelly’s criticisms of the sample size and composition in Loomis and West’s study are not completely relevant for driving studies. Although in any drug study care must be used in generalizing results to a broader population, the important issue here is that a group of people do exist, who probably do drive, and who are adversely affected by the drug. Wide differences in the personality make-up and driving skills of the various groups that are studied may lead, however, to contradictory results among experiments (Weatherall).

Only a few experiments on driving have been done in which alcohol and tranquillizers have been used in combination. Marquis used 800 mg. of meprobamate and less than one ounce of alcohol, and again found no impairment. This experiment was criticized by Zirkle on the grounds that common use of tranquillizers is chronic rather than acute, and that the alcohol was given in extremely small amounts and without respect to body weight. Zirkle gave 1,600 mg. of meprobamate per day for seven days and enough alcohol to produce an 0-05% concentration in the blood. Although he did not use a driving simulator test, he did find that, as compared with Marquis’ results, the meprobamate-alcohol condition resulted in poorer performance on all his tests than did either drug alone.

Zirkle makes the following statement, “According to the clinical judgments of two of the experimenters, the combination of alcohol with meprobamate produced more intoxication effects than alcohol alone in 16 of the 22 cases. On the day of the combined drug dosage, four of the subjects were quite obviously drunk. They showed marked muscular inco-ordination and little or no concern for the social proprieties. Nothing approaching this was observed in the alcohol condition. One of the subjects cried uncontrollably, and afterwards was largely amnesic for the period. Two could not walk without assistance” (p. 285).

Possibly partly on the basis of this change in general appearance, which agrees with the report of Greenhouse and
Pilot, Zirkle warns that, "physicians prescribing meprobamate should warn patients of the greater effect from drinking alcoholic beverages while taking the drug—especially if they are likely to operate motor vehicles or other complex machinery". However, the easy generalization from an experiment with no test of driving at all is something of a scientific non-sequitur.

Chlorpromazine was used in a very similar experiment which did include an AAA driving simulator by Zirkle and his group. Results were less dramatic but in the same direction. Greater impairment occurred for the combined drug condition than for either drug alone. Chlorpromazine was given at 200 mg. per day for one week, as it is customarily used, and alcohol in quantities to produce a blood alcohol level of 0.05%.

On the basis of these experiments, we may say that the usual therapeutic doses of tranquilizers, given either acutely or chronically, produce little or no impairment of driving performance, although the amount of dose, the time it is taken, and the individual response of the driver may complicate this picture. On the basis of one study, therapeutic chronic doses of meprobamate and a social dose of alcohol do markedly change behaviour, and, it is assumed, driving ability. While these findings are meagre and restricted to test situations, the studies do bring up certain terms in evaluating results of experiments on drugs and in constructing the experiments themselves.

Although alcohol is usually given in terms of body weight, none of the studies of driving and tranquilizers used this method of administration for tranquilizers. As a matter of fact, the Physician's Desk Reference specifies doses without reference to the size of the individual. This may partly account for the relatively few significant results, since the effect of such a procedure is to produce a wide range of effective doses among individuals; it leads to a large experimental error, or variability, and so reduces the chances of differences, whether they are large or small, attaining statistical significance. One way to handle this would be to do a regression analysis using subject's weight in place of dose. This would be equivalent to giving many doses. Although Zirkle et al. used a urine test to verify the presence of chlorpromazine, no adjustment of response for chlorpromazine levels in the urine was reported.

Alcohol experiments are acute in terms of administration of the drug; a single dose is given and observations are made at some point or points on the blood alcohol curve. Sometimes the subjects are maintained at a desired blood level by successive doses of alcohol. As a general rule, at least as far as driving studies are concerned, subjects are not maintained at blood levels by chronic or long-term administration of alcohol for days or weeks. By contrast, tranquilizer studies may be either acute or chronic. The rationale for acute v. chronic can be specified on the grounds of common use: alcohol is used in an acute manner by most people, while tranquilizers are usually used chronically. In general, an alcohol and tranquilizer experiment will be acute for alcohol and chronic for tranquilizer. This is not to say that there are not chronic users of alcohol, e.g. those who maintain an average daily level above zero, and who also use tranquilizers. These seem to me to be a special problem in alcohol research. On the other hand, some people do use tranquilizers in single doses, when needed. Interest in short-term effects, and their build-up, provides the reason for doing acute tranquilizer experiments.

In the chronic administration of a drug, time of testing is not important because the drug is brought to a relatively constant level by regular use over an extended period (e.g. one week for Zirkle et al.; Kelly et al., 21 days or so, etc.). However, as Weatherall points out, "it is commonly held that phenothiazines (e.g. chlorpromazine) do not exert their full effect in less than a month", and thus most of these experiments have not employed the drug long enough to reach its maximum effect. In general, one may expect quite a difference in results from an acute as compared to a chronic experiment, as a comparison of Zirkle's and Marquis' results would suggest. The length of time a drug has been given should be noted in comparing results of several studies. Chronic administration may lead to two opposing effects: one, a build-up of tolerance to the drug; and two, a cumulative effect and build-up of toxicity.

The time of testing after drug administration is an important consideration in experiments which study acute effects. Each drug has its optimal time of action. Thus, Loomis and West used test periods spaced at one-hour intervals for six hours after initial administration of the drugs.
Meprobamate first produced a detectable effect within two hours, whereas chlorpromazine did not until after four hours. The consideration of time in this experiment shows an appreciation of drug action not apparent in most of the driving and drug studies.

When large batteries of tests are given, which require an extended length of time to complete, it becomes possible for each test to be administered at effectively different doses, depending on the absorption curve and action of the drug. This means that some tests in the battery will be more favourably located to detect a significant drug effect. Large test batteries may also lead to fatigue, so that tests at the end of the battery are at a disadvantage compared to those at the beginning. If batteries are very long, it becomes almost hopeless to retest at frequent intervals.

Although large test batteries offer a broader search procedure, the use of a battery whose contents are selected because they are available in the laboratory can be expected to lead to a number of statistically significant results predicted by chance. Even an elementary hypothesis can serve as a central theme for the selection of tests in the battery. In addition, the fewer the hypotheses, the more attention can be given to each. In some papers there does not appear to be a sufficient development, aside from that loosely implied by what the test is supposed to measure, for including each test in the battery. One is often at a loss to explain their presence.

The same apparent lack of rationale appears in the use of statistical procedures. For example, some experimenters have turned out hundreds of t-tests for mean differences when a standard regression analysis might have shown a significant slope of response on dose, a much more sensitive and meaningful procedure. With this procedure, low doses that produce responses not significantly different from zero by the t-test may still contribute to the slope of the dose-response line. In other words, low doses may be effective and potentially dangerous when used with another drug; this effect may not be detectable by a t-test, but would be apparent from a significant slope.

It is difficult to determine the importance of observed impairment. To begin, it is not known how much deterioration is allowable for safe driving. Statistical significance means only that a found difference is likely to be a real and not a chance difference. Whether this difference is important or not is a separate problem. The problem is confounded when results are reported in various ways by different investigators, e.g. Bjerver and Goldberg report the degree of impairment (25–30% at 0-04-0-05% BAL), and Gelin and Wretmark use a frequency measure (at least one subject impaired at 0-03%). In addition, deviation from a control level may be significant statistically, and large enough to attract attention, but again evaluation of the change depends on the representativeness of the control level as an example of actual driving. A 25% deterioration from a very high level of performance may in no way compare in its consequences for safety to a 5% decrease at average performance levels. Besides, a given dose which produces a 25% deterioration at high levels of performance may, as far as anyone knows, produce less or more deterioration than 25% at average performance levels. At present there is no confident way of predicting the degree of deterioration from average to high, or high to average levels of performance.

Uhr and Miller comment further on the question of the importance of significant findings. They point out that the degree of deterioration under tranquillizers is extremely small and probably less than changes produced by fatigue, by sleep, diet and mood variations. Loomis and West's results agree with this interpretation: the deterioration produced by the tranquillizers was much less than that obtained with secobarbital (100 mg.), a barbiturate. Changes resulting from combined use of tranquillizers and alcohol are more likely to be both significant and important.

The result of using alcohol and a tranquillizer together is a problem in the joint action of drugs. Two terms frequently occur in the literature to describe the outcome of joint action: additive and synergistic. Additive means that the action of two drugs together is equivalent to the sum of the action of each drug alone. “Synergism” (from Webster, see Veldstra; Jawetz and Gunnison) “is the co-operative action of discrete agencies, such that the total effect is greater than the sum of the two taken independently.”

Even with these definitions it is difficult for an experimenter to determine whether one or the other has occurred. When drugs are combined, it is necessary to know the
dose–response function of each to predict even the simplest combined effect. For example, if the response to each drug is an accelerating function of dose, equally potent doses of each used jointly may give a response larger than otherwise expected. Mathematicians would refer to this effect as additive, although superficially it looks like potentiation or synergism. Another problem arises when curvilinear functions of dose are found, as is true for some problem-solving measures (Carpenter et al.), in which improvement in performance was observed at a low dose of alcohol, no change occurred at an intermediate dose, and deterioration appeared at a high dose. If an “additively acting” drug were given after the intermediate dose, the effect of such an intermediate dose would show itself as impairment. From the same example, two doses combined at levels which individually show improvement would have led to no change, and would have appeared to be antagonistic. Shape and direction of the relationship between response and dose of a particular drug depend on the response one observes and cannot be generalized with certainty to other responses. For example, in the problem-solving experiment (Carpenter et al.), three different types of curves were observed for measures taken simultaneously on the same behaviour.

Ultimately, criteria for determining the kind of joint action of drugs may be provided by mathematics and statistics. Hewlett and Plackett have developed such a formulation, based on two assumptions: one, drugs act at the same or different sites, and two, a drug either influences or does not influence the biological activity of the other. This formulation results in four possible kinds of joint action. One of these corresponds to the term additive (simple similar) action, and the other to synergistic (independent) action, although the authors use these terms sparingly and reluctantly. The remaining two types of joint action have not been described in detail yet. The general theory of joint action was developed for use with insecticides, but appears to be sufficiently general and compelling to be useful in our work. Such a model can be used to determine the nature of an observed response, additive or otherwise, and then to suggest the relationship between drugs, and between drugs and biological processes. An intriguing variation not mentioned in the theory of joint action is the possibility of a diffusely acting drug. That is, a drug whose site of action at some moderate dose is the central nervous system as a whole, rather than a system such as the reticular formation.

According to Berger’s recent statement (Uhr and Miller, Drugs and Behaviour), four different brain mechanisms have been hypothesized (cortex, limbic system, hypothalamus, and reticular formation) as the site of action of various tranquillizers. Kalant cites evidence that alcohol affects the reticular formation first, then the cortex. In other words, expert opinion is that different drugs act principally in different places. When drugs are combined, we have all the ingredients for the complex interactions covered by the theory of joint action of drugs. In theory, at least, the combination of alcohol and tranquillizer can be mild or devastating, and the quality and intensity of effect for a given amount of alcohol should depend on the locus of action of the tranquillizer that is used. One should be particularly cautious about drinking if one has recently changed tranquillizers, since the effects of one tranquillizer cannot be inferred from the effects of another.

**Summary**

We have reviewed the experimental papers on driving when alcohol, tranquillizers, or both are used. All results, but especially those with tranquillizers, are quite limited by the kinds of tests of driving in use. The evidence from alcohol experiments indicates that impairment of functions occurs at blood alcohol levels near 0.05%. Evidence for the effect of tranquillizers on driving skill is not clear, and changes, when they occur, are small. Only three papers were discovered in which alcohol and tranquillizers have been used together. One experiment in which a single mild dose of meprobamate was followed by a small amount of alcohol (one fluid ounce) produced no observable change in behaviour. Severe behavioural deterioration was reported in one paper when alcohol in small amounts (blood alcohol level: 0.05%) was consumed after one week of therapeutic doses of meprobamate; impairment was greater than with either drug alone. Similar but less drastic changes were reported for chlorpromazine under nearly identical conditions.

It is felt that the detection of drug effects would be increased if more thought was given to experimental and analytical
procedures. Problems in the interpretation of results were discussed. A mathematical theory of joint action of drugs, similar to that developed for use with insecticides, may prove helpful in determining the nature of interactions and pointing out in a general way the kind of mechanism which underlies them.

REFERENCES