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# Effects of Terfenadine and Diphenhydramine Alone or in Combination with Diazepam or Alcohol on Psychomotor Performance and Subjective Feelings

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**Summary.** The effects of single oral doses of terfenadine, diphenhydramine and placebo, alone or in combination with diazepam or alcohol, on psychomotor performance and subjective feelings were evaluated in a double-blind, crossover study in 20 normal male volunteers. Terfenadine 60, 120 and 240 mg had no effect on psychomotor skills and subjective feelings, whereas diphenhydramine 100 mg slightly impaired certain features of psychomotor performance and severely worsened subjective feelings. Terfenadine 120 mg did not influence the adverse effects of oral diazepam 10 mg or of alcohol 0.75 g/kg on psychomotor performance and subjective feelings. In contrast, diphenhydramine 100 mg significantly enhanced these effects of diazepam and alcohol.

**Key words:** Histamine antagonists, terfenadine, diphenhydramine, diazepam, alcohol, drug interactions, effects on psychomotor performance and subjective feelings.

Sedation is a common side effect of many antihistamines. It complicates or precludes their use by people engaged in activities requiring mental alertness, such as driving a car or operating dangerous machinery. Furthermore, the sedative effect is unpleasant to many patients and may reduce their compliance with a therapeutic regimen.

Terfenadine, a new histamine $H_1$-receptor antagonist, has been free of central nervous system side effects in pharmacological [1], toxicological [2] and clinical [3] studies. To evaluate further the lack of action of terfenadine on the central nervous system, the present study compared the effects of single oral doses of terfenadine, diphenhydramine and placebo, alone and in combination with diazepam or alcohol, on psychomotor skills and on subjective feelings.

## Material and Methods

### *1. Subjects*

20 normal, healthy, male volunteers (students) between 21 and 29 years of age (mean 24.8 ± 2 years) were selected after they had given informed written consent. Criteria for selection were: no history of drug allergy or incompatibility (including alcohol), no use of drugs for 4 weeks prior to the study, no use of drugs other than the test compounds during the study, no drinking of alcohol for 24 h prior to each test day. All subjects had to achieve a sufficient performance score during a one day training period before the actual drug study.

### *2. Design of Trial*

The study was conducted in 3 parts, as a double-blind, completely randomized, crossover, within-subject comparison of the treatment schedules listed in Table 1.

Between each treatment schedule there was a washout period of at least 48 h. The medication was administered orally to fasted subjects with 100 ml water.

In the terfenadine-alcohol interaction study, the alcoholic beverage was 40 vol. % vodka. The appropriate volume to give 0.75 g alcohol per kg body weight was calculated (e. g. 166.3 ml vodka per 70 kg) and was diluted with orange juice to a final volume of 480 ml. This beverage was served 30 min

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**Table 1.** Treatment schedules

| Part | Treatment schedule |
|---|---|
| 1 | Placebo<br>100 mg Diphenhydramine<br>60 mg Terfenadine<br>120 mg Terfenadine<br>240 mg Terfenadine |
| 2 | 10 mg Diazepam + Placebo<br>10 mg Diazepam + 100 mg Diphenhydramine<br>10 mg Diazepam + 120 mg Terfenadine |
| 3 | Placebo + 0.75 g/kg alcohol (one hour later)<br>100 mg Diphenhydramine + 0.75 g/kg alcohol (one hour later)<br>120 mg Terfenadine + 0.75 g/kg alcohol (one hour later) |

after drug administration and had to be drunk within 30 min.

### 3. *Assessment Schedules*

Each test period was started at 8 a. m., and assessments were made before and 2 and 4 h after drug administration. Subjects were kept in a closed unit in order to observe possible adverse reactions. They were not isolated from each other during the intervals and were allowed to communicate, to play cards, to read, or even to sleep, if desired.

### 4. *Psychomotor Performance*

The following tests were employed:

*Vienna Determination Apparatus*[1] [22, 28, 31, 32, 33]. The unit evaluates reaction time, reaction reliability and performance capacity under a constant work load. The subjects must respond to 180 optical (five different colors) and acoustic (two different sounds) signals of 0.7 s duration by pushing knobs, key buttons and foot pedals. Correct fast reactions (within 0.7 s) and correct delayed reactions (after 0.7 s) are automatically recorded.

*Vienna Reaction Apparatus*[1] [22, 28, 32, 33]. The unit records automatically the time taken by the subject to press a key board with one hand when a series of color signals is shown (single reaction time), or when a series of color and acoustic signals are given (choice reaction time).

*Ball Cylinder Test*[2] [34]. Subjects are asked within 2 min to fit as many steel balls of different sizes into holes in a mantle which covers a rotating cylinder that contains holes into which the balls fit. Scores are automatically recorded.

*Critical Flicker Frequency (CFF)* [19]. The point at which a flickering light gives rise to the subjective sensation of a steady light is estimated.
Threshold is measured in HERTZ (cycles/s). Decreased CFF sensitivity is reflected by decreased (lower) HERTZ values.

*Letter Tachystoscope.* At each test 3 slides with different configurations of 9 letters are shown, each for 0.4 s, and the subjects are requested to write down what they have perceived.

*d2 Test.* This test evaluates the course of alertness. In long series of letter configurations special configurations have to be crossed out as rapidly and faultlessly as possible.

Before the study started, all subjects were trained for a full day in order to reach their maximal performance level.

### 5. *Self Evaluation Scales for Subjective Feeling*

Subjects were asked to grade their subjective feeling on 4 different 9 point visual scales:
Scale A: ranging from "I feel very fresh" (1) to "I feel very tired" (9)
Scale B: ranging from "I feel very well" (1) to "I feel very ill" (9)
Scale C: ranging from "I feel lively" (1) to "I feel dull" (9)
Scale D: ranging from "I feel not drunk" (1) to "I feel drunk" (9)

### 6. *Statistical Evaluation*

Non parametric tests were used.

*Psychomotor Performance Variables.* Since these variables were of cardinal type, the differences between pre-drug values were compared by Pratt's signed rank test [4, 5]. The differences between treatments were compared by Stegie's matched-pairs differences-W-test [6].

*Subjective Feeling Scores.* These test variables were of ordinal type. Pre-drug and post-drug scores were

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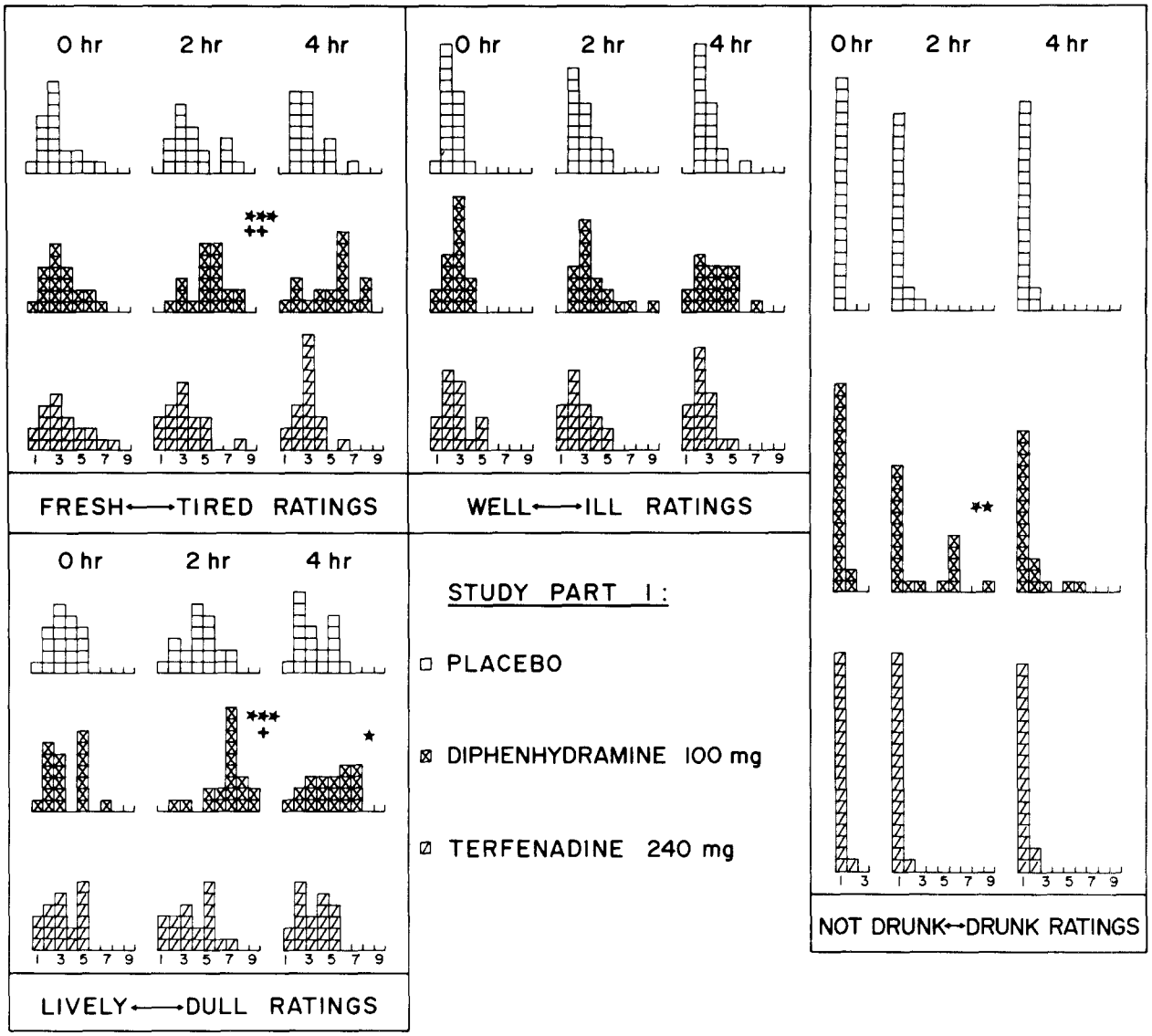


**Fig. 1.** Changes in subjective feelings. Each box represents the rating of one subject. Significant differences from pre-drug state: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ Significant differences from placebo: + $p < 0.05$, + + $p < 0.01$

compared by Dixon and Mood's sign test [7]. Differences between treatments were compared by Buck's matched-pairs differences signed rank test [8].

## Results

*Part 1*

No dose of terfenadine or placebo significantly decreased psychomotor performance. In fact, after administration of placebo and of each of the 3 doses of terfenadine, performance in some tests showed significant improvement compared to pre-drug values. No improvement in performance ever occurred after administration of diphenhydramine.

Compared with pre-drug values and placebo, diphenhydramine significantly impaired subjective feeling on 3 scales (Fig. 1). In contrast, no dose of terfenadine had any effect on subjective feelings.

*Part 2*

A single oral dose of diazepam 10 mg produced no significant change in psychomotor performance, except for a significant decrease in critical flicker frequency, and a decrease (improvement) in "choice reaction time" in the Vienna reaction apparatus test

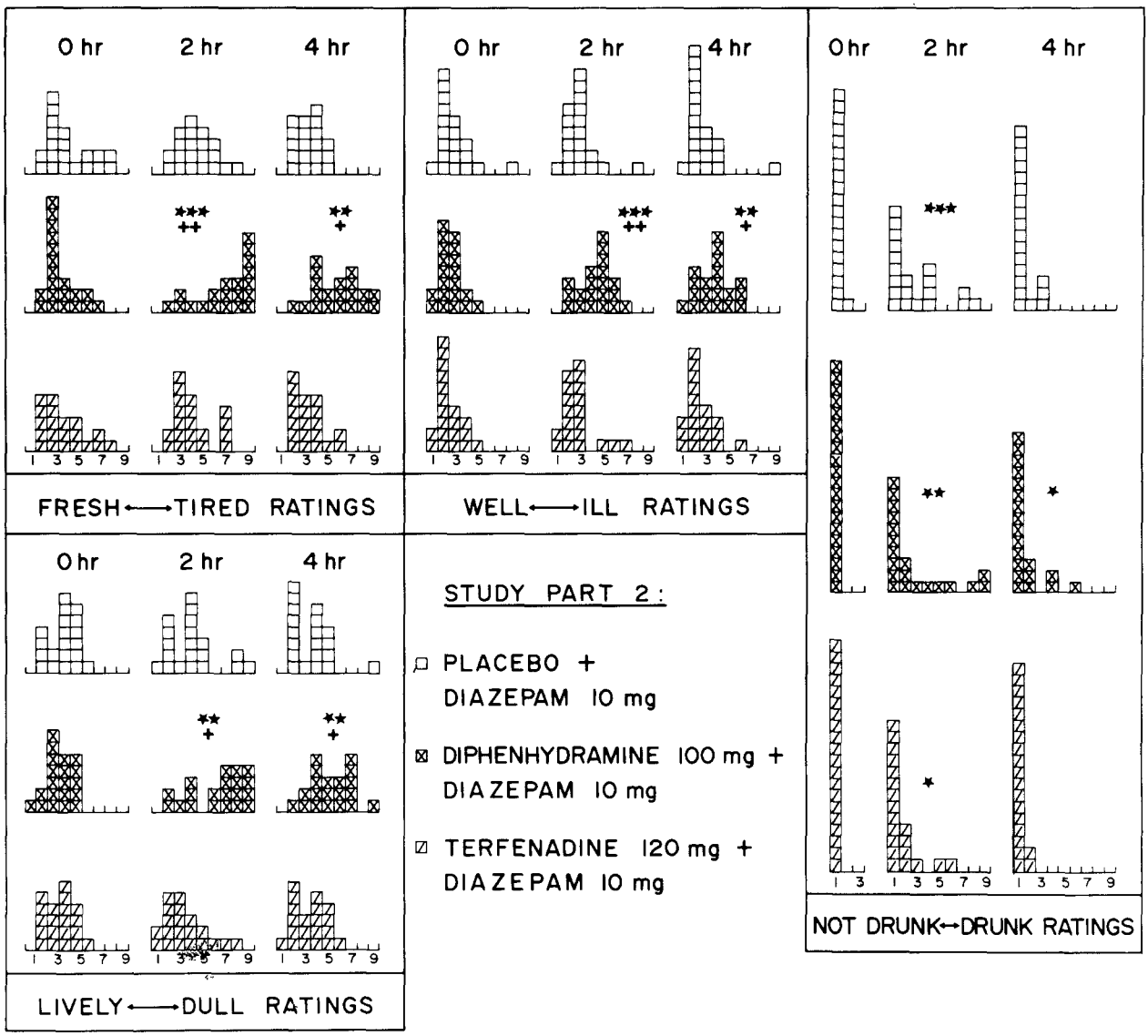


**Fig. 2.** Changes in subjective feelings. Each box represents the rating of one subject. Significant differences from pre-drug state: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ Significant differences from placebo and diazepam: + $p < 0.05$, ++ $p < 0.01$

(Table 2). The addition of terfenadine 120 mg to this dose of diazepam had no effect. In marked contrast, concomitant oral administration of diazepam 10 mg and diphenhydramine 100 mg significantly decreased performance at 2 h after drug application in all tests, except in the tachystoscopic test. Even at 4 h, "single reaction time" in the Vienna reaction apparatus test was still significantly increased.

Diazepam 10 mg, and diazepam 10 mg plus terfenadine 120 mg, had no effect on subjective feelings evaluated by 3 scales (Fig. 2). By contrast, the combination of diazepam and diphenhydramine caused significant impairment at 2 and 4 h after drug ingestion compared to pre-drug values and to diazepam alone. A significant feeling of drunkenness occurred 2 h after administration of diazepam alone and in combination with terfenadine or diphenhydramine. However, only after concomitant ingestion of diazepam and diphenhydramine was this feeling still present after 4 h.

*Part 3*

Performance in the Vienna determination apparatus test decreased significantly ($p < 0.05$) 2 h after administration of alcohol plus diphenhydramine, but not after alcohol alone, or after alcohol plus terfenadine. Reaction time to color signals in the Vi-

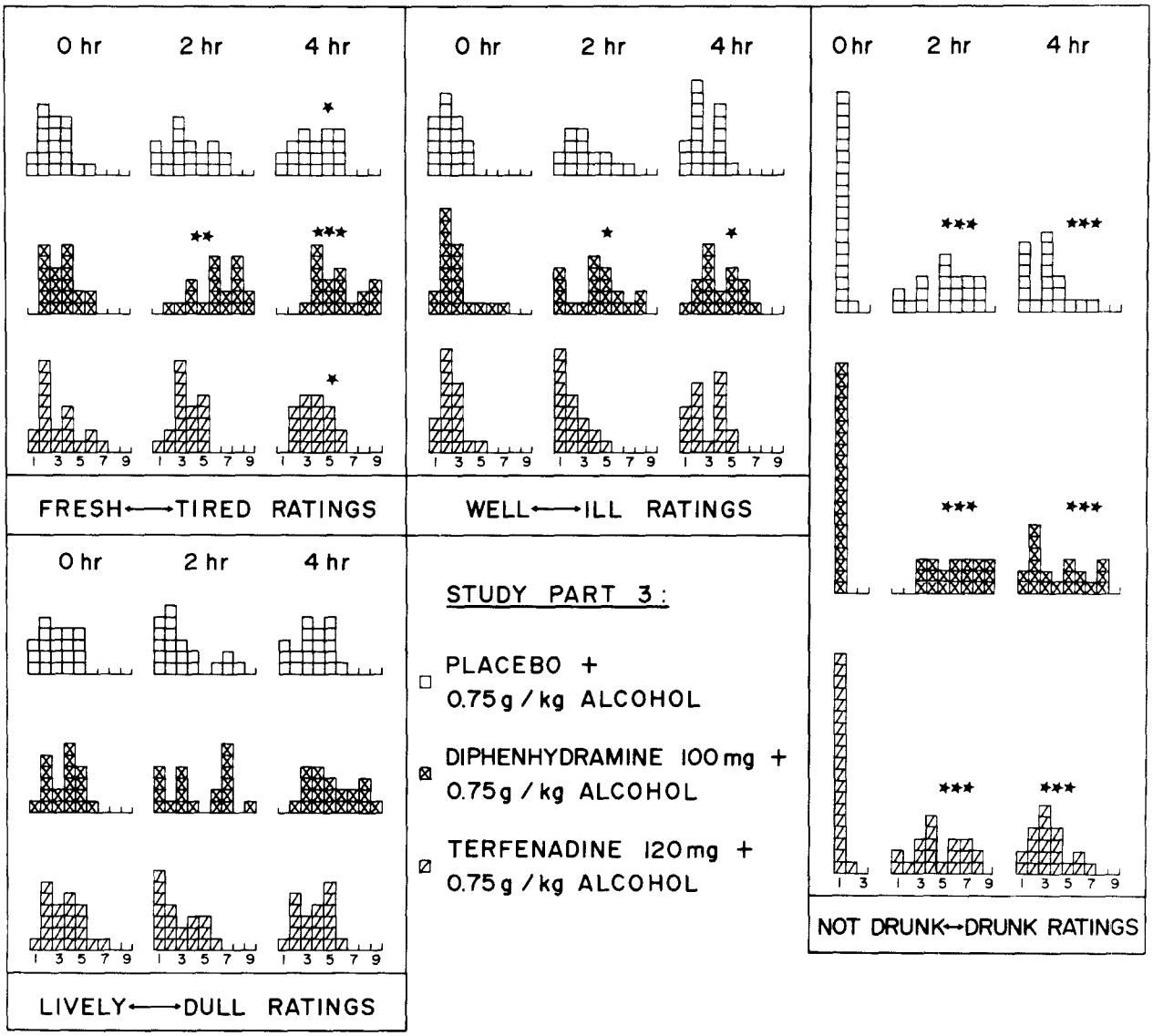


**Fig. 3.** Changes in subjective feelings. Each box represents the rating of one subject. Significant changes from pre-drug state: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

**Table 2.** Part 2 – Changes[a] in psychomotor performance

| Treatment | Comparison | Vienna determination apparatus[b] | | Vienna reaction apparatus[b] | | Ball cylinder Test | CFF[b] | Tachysto-scope | d2 Test |
|---|---|---|---|---|---|---|---|---|---|
| | | CFR | CDR | SR | CR | | | | |
| Diazepam 10 mg + Placebo | pre-drug/2hours post drug | 0 | − | − | 0 | − | −*** | 0 | − |
| | pre-drug/4hours post drug | − | + | 0 | +* | 0 | −*** | 0 | 0 |
| Diazepam 10 mg + Diphenhydramine 100 mg | pre-drug/2hours post drug | −* | −* | −*** | −* | −*** | −* | 0 | −*** |
| | pre-drug/4hours post drug | − | − | −* | 0 | − | −* | 0 | − |
| Diazepam 10 mg + Terfenadine 120 mg | pre-drug/2hours post drug | 0 | 0 | 0 | 0 | − | −** | 0 | 0 |
| | pre-drug/4hours post drug | 0 | 0 | 0 | 0 | − | −** | 0 | 0 |

[a] Symbols:
0 = no change; + = improvement; − = impairment
* = change statistically ($p < 0.05$) significant
** = change statistically ($p < 0.01$) significant
*** = change statistically ($p < 0.001$) significant

[b] Abbreviations:
CFR = Correct Fast Reactions
CDR = Correct Delayed Reactions
SR = Single Reactions
CR = Choice Reactions
CFF = Critical Flicker Frequency

enna reaction apparatus test, scores in the ball cylinder test and in the d2 test decreased significantly ($p < 0.05$) in all three groups. There was no significant change in critical flicker frequency sensitivity or in tachystoscopic perception.

Significant change in subjective feelings after 2 h, as measured by the "fresh-tired" ratings, occurred only in the group to whom both alcohol and diphenhydramine had been administered (Fig. 3). After 4 h the change was pronounced in this group, but in the alcohol plus placebo and the alcohol plus terfenadine groups it was much less marked and the groups did not differ from each other. Only alcohol plus diphenhydramine treatment caused significant impairment of subjective feelings judged by the "well-ill" scale. There was no statistically significant difference between the 3 treatment groups in the drunkenness ratings. However, high (> 4) drunk ratings were more than twice as frequent 4 h after alcohol plus diphenhydramine than after the other treatments (Fig. 3).

## Discussion

In an initial controlled clinical study of terfenadine, effective histamine $H_1$-receptor blocking doses did not have depressant action on the central nervous system [3]. The present study confirms the failure of terfenadine to impair psychomotor performance or adversely to affect subjective feelings. Neither the usual therapeutic dose of terfenadine (60 mg) nor doses two or four times larger could be distinguished from placebo. In this regard terfenadine contrasted markedly with another antihistamine, diphenhydramine, of which 100 mg was given as the positive control [9, 10].

The results of this study suggest that in the controlled experimental evaluation of central nervous system side effects of drugs it is desirable not only to measure psychomotor performance, but also to assess subjective feelings. The central nervous system action of diphenhydramine 100 mg was strikingly apparent in its effects on subjective feelings, but it was not clearly reflected in any deterioration of psychomotor performance. Similar findings have previously been reported [11, 12].

All subjects were trained in performance of the psychomotor tests for a full day before the study started. It is not clear whether the improvement in psychomotor performance commonly observed to a similar extent both after administration of placebo and terfenadine resulted from further learning by practice, was related to the time of day, or whether it represented a true placebo effect. In any case, the finding that no such improvement ever occurred after diphenhydramine administration very probably represents objective evidence of central nervous system depression.

The effects of diazepam and other benzodiazepines [9, 13–24], and of alcohol [11–16, 22, 23, 25–30] either alone or together, on tests of psychomotor performance and on subjective feelings have been established in numerous studies. Similarly, it is known that coadministration of diphenhydramine and other antihistamines can enhance the actions of alcohol [11, 12, 26, 27]. This was also clearly shown in the present study. The failure of terfenadine in twice the therapeutic dose to increase the impairment of psychomotor performance and subjective feelings by diazepam or alcohol is further evidence of its lack of effect on the central nervous system.

It appears that in the terfenadine molecule histamine $H_1$ receptor antagonist action and central nervous system actions have been largely or totally dissociated. It seems probable that the common central nervous system side effects of many antihistamines will not be a problem during clinical use of terfenadine. Further clinical experience will establish whether the dangerous central effects of overdosage with other antihistamines are also absent in the case of terfenadine.

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