Abstract. Naive, non-hungry, non-thirsty rats ingested inordinate amounts of a sweetened milk solution when given their first opportunity to drink the solution while under the influence of benzodiazepine drugs. Among many other drugs tested, only phenobarbital gave a similar, although clearly weaker, effect. The test provides a simple, rapid, sensitive, and specific screen for benzodiazepine-like drugs. The effects were interpreted in terms of these drugs overcoming (disinhibiting) a rat’s natural aversion to an unfamiliar food substance without at the same time greatly sedating the animal.

Key-Words: Screening Method — Benzodiazepine Drugs — Response Disinhibition.

Available animal tests for benzodiazepine drugs suffer from definite failings. These methods have been classified (Hanson and Stone, 1964) into four basic types depending on the behavioral end-points studied: taming actions, anticonvulsant effects, attenuation of conditioned conflict, and augmentation of food intake by hungry rats. Some of these methods, like those based on taming actions, tend to be unreliable, since they depend heavily on subjective judgments. Others, like the conditioned conflict methods (Geller and Seifter, 1960) are unable to handle large numbers of compounds. Most important, none of these methods is specific; thus, none can differentiate easily, if at all, benzodiazepine-like drugs from mere sedatives and anti-convulsants.

In this paper we describe a simple method which overcomes these problems to a large degree. It is based on the fact that non-deprived rats greatly increase their consumption of a strange, but very palatable, liquid (sweetened condensed milk) under the influence of benzodiazepine drugs. The method bears some resemblance to the older procedure which measured food intake by hungry rats. However, this resemblance is merely superficial because the present method yields results which are quantitatively much larger, and qualitatively much more specific.

Materials and Methods

Subjects. Male albino rats of the Holtzman strain are used. Our weekly standing order specifies that the rats should weigh between
200—210 g in body weight at the time of shipment. Upon arrival, they are housed in normal laboratory cages, eight rats per cage, for at least three days before the first groups are tested. The final groups from each weekly shipment are tested no later than eight days after arrival. Each rat serves only once in the procedure, and after use is either discarded or shifted to another testing program. At no time are the rats given any special handling or training, nor are they ever placed under any condition of dietary deprivation.

**Apparatus.** The tests are carried out with a standard metabolism cage rack. Our rack (Acme Metal Products, Inc.) has 24 individual cages on it; consequently, we run three treatments per test with eight rats serving under each treatment. The milk solution is prepared fresh each day, using one part Borden's Sweetened Condensed Milk to two parts water. Hung on the outside of each individual rat's cage is an inverted 50 ml glass graduate fitted with a rubber stopper and metal licking tube. The graduates (Pyrex No. 8101) are calibrated in red ink and can be read easily to the closest 0.5 ml even when filled with milk. The hole in the tip of each metal licking tube is about 2.25 mm in diameter; prior to use, the tip of each tube had been polished to remove any roughness or burrs.

**Drug Administration.** Water-soluble drugs are dissolved in deionized water; if insoluble, even if only at high doses, all doses are suspended in 0.2% methocel. The oral route of administration is used routinely, along with a 30-minute absorption period. In the case of most agents, the first dose tested is usually 40 mg/kg. Agents which show activity at the initial dose are tested further at lower and/or higher doses as the mean ingestion scores and gross behavioral effects warrant. In the work reported here, the doses refer to the total drug (base plus salt).

**Procedure.** Non-deprived rats are dosed orally and then placed into individual metabolism cages. 30 min later, the tip of a licking tube is inserted into each cage; this signals the start of the test. Milk intake is recorded after one hour. All aspects of the testing procedure are carried out in the rats' home cage room.

**Results**

Rats treated with water or with 0.2% methocel solution normally consume less than 5.0 ml per rat as a group. The effects obtained under various doses of different drugs are shown in the Table 1. For comparison

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1 Because of the possibility of strain differences, the present results are meant to apply only to the male, albino, Holtzman rat. However, limited tests have been run on other strains: Sprague Dawley, Charles River, and Carworth of Michigan. These tests indicated that at least these strains give results which are fairly comparable to those in the Holtzman rat.