Effects of Aspirin on Gastric Mucosae of Albino Rat and Mongolian Gerbil (*Meriones unguiculatus*)

CLARENCE H. MORRIS*, JOHN E. CHRISTIAN, and WARREN G. HANSEN

Abstract □ When albino rats were orally administered aspirin in buffer at pH 4.60 at a dose level of 50.0 mg./kg. body weight, all of the animals developed gastric erosions and bleeding within 2 hr. Under the same conditions and at the same dosage, Mongolian gerbils failed to develop these lesions. At higher dose levels of 100 and 200 mg./kg., some gerbils developed mild to moderate gastric lesions with some bleeding.

Keyphrases □ Aspirin—effect on gastric mucosae, albino rat, Mongolian gerbil □ Gastric mucosae—effect of aspirin, albino rat, Mongolian gerbil □ Aspirin—inducing development of gastric erosions and bleeding, albino rat, Mongolian gerbil

It has been known for more than 50 years (1) that the oral administration of aspirin and closely related compounds results in erosions of the gastric mucosa and bleeding from the site of the lesion. These erosions were observed in human subjects (1, 2), dogs (3), cats (4), guinea pigs (5), and albino rats (6). Major biological differences between species with respect to this pathological response to aspirin have not been described.

In recent years, the Mongolian gerbil (*Meriones unguiculatus*) has become increasingly popular as a laboratory animal because of its docility, curiosity, and tractability (7). Therefore, during present studies concerned with mechanisms of aspirin-induced gastric lesions, it became of interest to compare the responses of the gastric mucosae of the Mongolian gerbil and the albino rat to aspirin.

MATERIALS AND METHODS

Twenty six male albino rats[1], weighing about 250 g. (range 200–300 g.), were divided into two groups. The experimental group, consisting of 18 animals, received individual doses of 50 mg. aspirin/kg. body weight; the control group of eight animals received the dose medium only.

Male gerbils[2], weighing about 58 g. (range 50–65 g.), were divided into three experimental groups and a control group. One group of 19 animals received individual doses of 50 mg. aspirin/kg. body weight, the second group of 7 received 100 mg. aspirin/kg. body weight, and the third group of 11 received 200 mg. aspirin/kg. body weight. A control group of 20 gerbils received the dose medium only.

All animals were fasted for at least 15 hr. prior to administration of the aspirin or dose medium. During the fast, they were allowed water *ad libitum*. Water was withdrawn at the time of administration of the drug or dose medium.

The chemical purity of the aspirin was established according to the procedure outlined in the USP (8). Eighty-five milligrams of pure aspirin was dissolved in 5.95 ml. of 0.15 *M* citrate buffer, pH 5.60. The pH of this mixture after solution of the aspirin was 4.60. A similar buffer solution for control animals was adjusted to pH 4.60 with the aid of the glass electrode and careful addition of 1 *N* HCl. Enough aspirin solution was administered to each experimental animal to give a dose of 50, 100, or 200 mg./kg. body weight. Corresponding volumes of buffer solution were administered to control animals. These solutions were administered orally to the animals by means of a No. 16 curved steel oral catheter which was dipped in mineral oil for lubrication.

Exactly 2 hr. after administration of the dose solution, each animal was killed by etherization. The stomach was removed, opened along the line of lesser curvature, stretched, and pinned on a large rubber stopper. The mucosal surface was washed with 0.9% saline to remove any mucous, ingested feces, or other debris. Each stomach was then examined grossly and graded on an eight-point scale developed by Morris *et al.* (9) with respect to the number and size of lesions present. (A rating of 1 corresponds to a normal stomach; a rating of 8 corresponds to the most severe condition, representing more than 10 lesions, one or more of which is larger than 1 mm. in diameter. Ratings 2 through 7 lie between the two extremes in severity.)

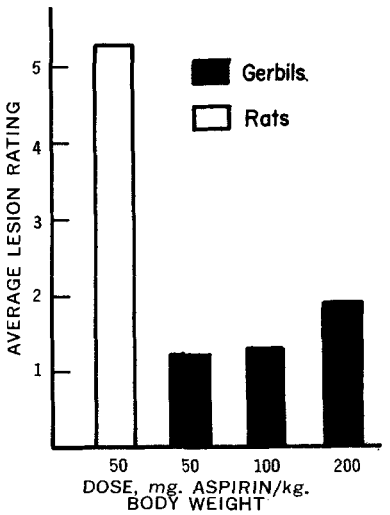

Figure 1—*Average lesion ratings of rats (that received individual doses of 50 mg. aspirin/kg. body weight) compared with average lesion ratings of gerbils (that received individual doses of 50, 100, or 200 mg. aspirin/kg. body weight).*

RESULTS AND DISCUSSION

The results are presented in Fig. 1, which shows the average lesion rating of the rats and gerbils plotted *versus* dose level. All of the rats that received aspirin developed lesions in the secretory epithelium of the gastric mucosa.

By contrast, 16 of the 19 gerbils in the first experimental group, which received 50 mg./kg. body weight, could not be distinguished from their controls. The gastric mucosae of these animals appeared normal in every respect on careful gross examination. In three of the gerbils that received this dose of aspirin, mild erythema was seen in the secretory epithelium, but no lesions of any kind could be found.

Of the second experimental group of gerbils, which received individual doses of 100 mg. aspirin/kg. body weight, one stomach was graded 3 (less than five lesions, all of which are less than 1 mm. in diameter) on the rating scale. All others of this group were entirely normal and indistinguishable from the controls. Of the 11 gerbils in the third experimental group, which received 200 mg. aspirin/kg. body weight, one was graded 4 (less than five

[1] Holtzman Rat Co., Madison, Wis.
[2] Chick Line, Vineland, N. J.

lesions of which one or more are larger than 5 mm. in diameter) and four were graded 3 on the rating scale. The remaining six stomachs were normal.

These observations indicate that the Mongolian gerbil is less susceptible to the induction of gastric lesions by aspirin than the Holtzman albino rat. The biological basis for the observed difference in resistance is not revealed by the present study. It is, however, clear that a dose level of aspirin causing gastric mucosal erosion in all of the male albino rats that received it did not cause such erosion in those male Mongolian gerbils to which it was administered. Higher dose levels do result in lesion formation in the gerbil, with a direct relationship between incidence and dose. However, even at a dose level fourfold higher than that causing lesions in all rats that received it, only 5 of 11 gerbils exhibited lesions, the severity of which was slight to moderate.

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Isolation and Identification of 8-(2-Diphenylmethoxy-*N*-methylethylamine)-1,3-dimethylxanthine from Dimenhydrinate

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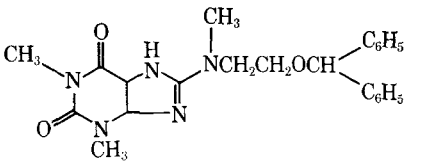
Abstract □ Differences in solubility and in rate of solubility from previously tested chemical lots were observed in a dimenhydrinate chemical evaluated by the tests and specifications in the official monograph. An impurity was isolated from the lot in question and was identified as 8-(2-diphenylmethoxy-*N*-methylethylamine)-1,3-dimethylxanthine based on spectral and elemental data.

Keyphrases □ 8-(2-Diphenylmethoxy-*N*-methylethylamine)-1,3-dimethylxanthine—isolation, identification from dimenhydrinate □ Dimenhydrinate—isolation, identification of 8-(2-diphenylmethoxy-*N*-methylethylamine)-1,3-dimethylxanthine □ Impurity of dimenhydrinate—isolation, identification of 8-(2-diphenylmethoxy-*N*-methylethylamine)-1,3-dimethylxanthine

In a routine analysis of dimenhydrinate chemical according to the tests and specifications in the USP XVII monograph, it was observed that one lot did not completely dissolve in alcohol. Also, its solubility in water, which is the first step in the diphenhydramine assay, was less than complete. In both instances, a hazy solution resulted. However, except for these slight discrepancies, the chemical met the requirements detailed in the monograph. Previous lots dissolved rapidly in the solvents mentioned, while this lot had a poor rate of solubility.



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Differential thermal analysis revealed one major endotherm at 105° which was identical to previous lots tested. The X-ray diffraction pattern was also the same as previous lots, ruling out polymorphism as a possible explanation for the solubility difference. The thin-layer chromatogram had spots corresponding to the diphenhydramine and 8-chlorotheophylline moieties and a

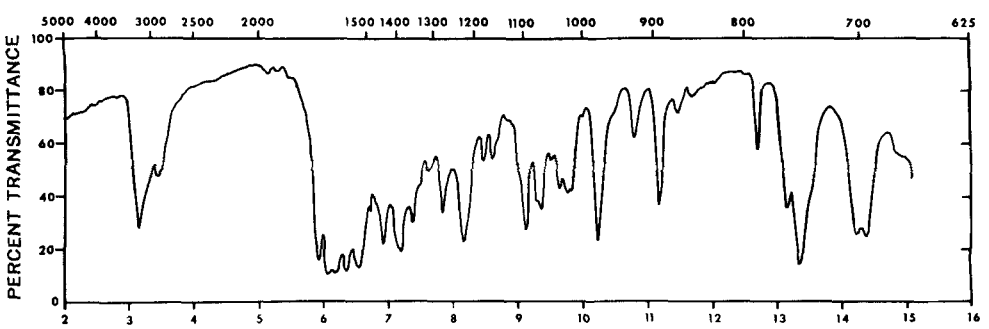

Figure 1—*IR spectrum o unknown.*