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Comparison of the Antipyretic Action and Toxicity of D-Glucono-Para-Phenetidin and Acetphenetidin.

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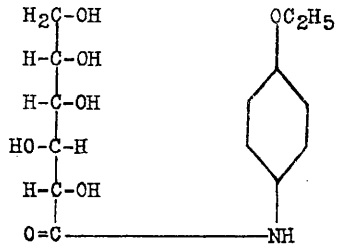
D-Glucono-Para-Phenetidin* is a gluconic acid derivative of phenetidin, having the following structure:



Glucono-phenetidin. This is analogous to acetphenetidin, the acetic acid derivative. The structural similarity of these 2 compounds suggested a comparison of their antipyretic activities, using fevered rabbits, and of their toxicities, using white rats.

Antipyretic Action. The 2 drugs were tested on rabbits fasted for 48 hours and without water for 24 hours, which were fevered by the injection of hay infusion. Five experiments were conducted. The procedure of a typical experiment was as follows: 14 animals were selected and rectal temperatures taken. Two animals were set aside as normal, room temperature controls, and received no further treatment. The remaining 12 animals, weighing between 2 and 3 kg., were injected subcutaneously with 5 cc. per kg. of a 10% hay infusion, incubated for 24 hours at 37°. Two hours after injection, rectal temperatures were again taken, and the 3 animals with the poorest fevers were discarded. The 9 remaining animals, which had fever rises ranging from 0.80° to 2.30° C., were then separated into 3 groups: (a) Three animals were kept as fever controls; (b) 3 animals were treated with glucono-phenetidin; (c) 3 animals were treated with acetphenetidin. The drugs were suspended in 50 cc. of 1% acacia solution, and were fed by stomach tube. The 3 fever control animals received a similar administration of acacia solution. Rectal temperatures were taken periodically over 6 hours after the

* The Glucono-phenetidin used in this study was kindly furnished by Charles Pfizer & Co., Inc., New York.

feeding. In the first experiment a dosage of 0.300 gm. per kg. of acetphenetidin and a corresponding molecular weight (7:4) of glucono-phenetidin (0.525 gm. per kg.) were used; these doses proved to be about minimal. In one of the remaining experiments, doses of 0.500 gm. per kg. of acetphenetidin and 0.875 gm. per kg. of glucono-phenetidin were used, and in the remaining 3 experiments, respective doses of 0.600 gm. and 1.050 gm. were used.

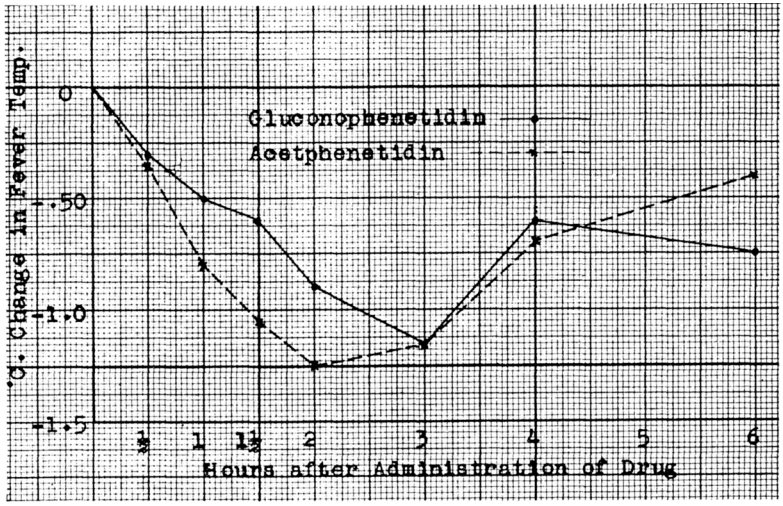


FIGURE 1.
Comparison of antipyretic activity of glucono-phenetidin and acetphenetidin on fevered rabbits. Summary of 3 experiments (see text), glucono-phenetidin 1.050 gm. per kg.; acetphenetidin 0.600 gm. per kg.

The data in each group for each experiment were found to be consistent and average values could therefore be taken, the temperature changes in the room- and fever-control animals being used to correct the temperature changes produced by the drugs. Figure 1 graphically presents such average values for the 3 experiments with the largest dose (1.050 gm. per kg. of glucono-phenetidin, and 0.600 gm. per kg. of acetphenetidin). This represents 9 animals for glucono-phenetidin, 8 for acetphenetidin, 7 fever controls, and 7 normal controls. The ordinate of the curves indicates the corrected average changes in the initial fever temperatures, which are represented by the zero mark; the horizontal line through this mark, indicating the corrected average fever control temperatures. The curves show very little difference in the antipyretic action of the 2 drugs. The one experiment, with doses of 0.875 gm. of glucono-phenetidin and 0.500 gm. per kg. of acetphenetidin, compared with

the larger doses of the preceding experiment, gave a slower but similar effect for the 2 compounds.

Toxicity. These studies were made on rats, after a one-day fast, fed by stomach tube with emulsions of each of the 2 drugs in 5% acacia solution. Glucono-phenetidin was used on 20 animals with doses ranging up to 50 gm. per kg. of body weight. All survived the treatment for from 4 to 6 days (the length of the period of observation) without any other signs than an occasional immediate slight depression, apparently due to the large volume which was fed (in a few cases above 5 cc.). It is conceivable that the larger bulk of the glucono feedings may have diminished its absorption mechanically, and so decreased its toxicity; but no toxicity was observed even with doses 10 times as large as those for acetphenetidin.

Definite signs of toxicity were observed with acetphenetidin. The drug was fatal only slowly (more than 4¼ hours). Toxic signs frequently occurred within 2 hours with the higher doses, and more slowly with the smaller doses. Seventeen animals were fed. The minimal fatal dose was about 4 to 6 gm. per kg. by stomach tube. Post mortem examination of 2 animals disclosed only slight pulmonary edema and no distinctive lesions. Death seemed to be due essentially to some blood dyscrasia which produced cyanosis. Other symptoms were a slow deep respiration with occasional wheezing and dripping of clear fluid from the nose, diarrhea and coma, with occasional muscular twitchings of a clonic nature.

Summary. The antipyretic action of glucono-phenetidin in equimolecular proportions is about equal to the action of acetphenetidin when tested on rabbits fevered with injections of hay infusion. Glucono-phenetidin is non-toxic to rats in doses up to 50 gm. per kg., whereas acetphenetidin manifests occasional toxic symptoms in doses as low as 4 gm. per kg., and was fatal in 3 out of 5 animals with a dose of 6 gm. per kg. This indicates a definitely wider range between therapeutic and toxic dose for glucono-phenetidin than for acetphenetidin.