

induced in mice following the subcutaneous injection of methylcholanthrene for many generations is hereditary dwarfism. This condition is inherited as a recessive. The relation of this mutation to the general problem of parallel induction is briefly indicated. Thus it is becoming more obvious that both non-

genetic and genetic biological variants are being produced in mice by methylcholanthrene. The mechanism involved may be different for the different variants obtained but perhaps there may be a common denominator in them all.

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### Effect of Muscular Fatigue on Histamine-Provoked Ulcer with Observations on Gastric Secretion.

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Complete physical rest is frequently mentioned by internists as a valuable adjunct in the medical management of peptic ulceration. This precept has been derived primarily from clinical observation as there are few if any experimental studies in recent medical literature which deal with the effects of muscular fatigue on alterations in gastrointestinal tract function particularly as they pertain to the ulcer diathesis.

It is the purpose of this report to indicate our observations on the effect of moderately severe muscular fatigue on the incidence of the histamine-provoked ulcer and upon gastric secretion in dogs.

*Method of Study.* Experiment 1. Fifteen healthy, dewormed dogs weighing from 26 to 54 lb, of young to medium age, were run from 3 to 4 hours consecutively each day in the morning on 5 to 6 successive days on an electrically driven endless belt treadmill. The dogs were allowed a 10-minute rest period each hour and water *ad lib*. The treadmill speed was calculated at 1.5 to 2.0 miles per hour which amounts to a brisk walking pace for the average sized dog. The slope of the treadmill was varied between an incline of 5 to 20° from horizontal depending on the

dogs' physical condition. Just prior to being placed on the treadmill each day, the dogs were given an injection intramuscularly of 30 mg of histamine base-in-beeswax mixture prepared after the method of Code and Varco.<sup>1</sup> The dogs were fed a diet of horsemeat, milk, dog biscuit each day after finishing their period on the treadmill. Rectal temperatures were taken before the start of the exercise and after each hour of exercise as a gross indication of the degree of muscular effort.

As a control series, 13 animals of comparable size, age, and health were fed and injected daily with histamine as above, but were not run on the treadmill. In addition 2 dogs were run on the treadmill as above, but were not given histamine. In these 2 animals the effect of the muscular exercise on hemoglobin, hematocrit, leukocytes differential count, and blood sugar was studied. All animals were sacrificed with examination of their gastro-intestinal tracts at the end of their test period of 5 to 6 days on the treadmill and/or 5 to 6 consecutive daily intramuscular histamine-in-wax injections.

Experiment II. Studies on gastric pouch secretion were made using 2 Heidenhain-type pouches made over one year prior to the onset of these experiments. Both animals used were

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<sup>1</sup> Code, C. F., and Varco, R. L., *Proc. Soc. Exp. Biol. and Med.*, 1940, **44**, 475.

TABLE I.  
Production of Ulcer in Dogs Following Muscular Fatigue.  
(30 mg histamine-base in Beeswax daily.)

| Dog No. | Initial<br>wt, lbs | Days on<br>treadmill | Total<br>hrs on<br>treadmill | No. of<br>hist. inj. | Wt loss<br>lbs | Results                             |
|---------|--------------------|----------------------|------------------------------|----------------------|----------------|-------------------------------------|
| 888     | 39                 | 6                    | 23                           | 6                    | 4              | 3 gastric ulcers                    |
| 902     | 32                 | 6                    | 20.5                         | 6                    | 3              | Negative G. I. T.                   |
| 909     | 37                 | 5                    | 18                           | 5                    | 3              | Duod. ulcer and erosions            |
| 916     | 34                 | 5                    | 18.5                         | 5                    | 2              | Multiple duod. and jejunal erosions |
| 948*    | 40                 | 2                    | 6                            | 1                    | —              | Duod. and jejunal erosions          |
| 951     | 37                 | 5                    | 19                           | 6                    | 3              | Large duod. ulcer, antral erosions  |
| 956     | 26                 | 5                    | 19                           | 6                    | 7½             | Large duod. ulcer, antral erosions  |
| 967     | 43                 | 5                    | 17                           | 6                    | 6½             | 2 duod. ulcers                      |
| 979     | 45                 | 5                    | 20                           | 5                    | 4              | Negative G. I. T.                   |
| 994     | 40                 | 5                    | 19                           | 5                    | 2              | Duod. erosions                      |
| 7       | 32                 | 3                    | 12                           | 3                    | 5              | Died, perforated duod. ulcer        |
| 16      | 43½                | 5                    | 20                           | 5                    | ½              | Negative G. I. T.                   |
| 38      | 54                 | 5                    | 20                           | 5                    | 4              | Duod. erosion                       |
| 59      | 44                 | 5                    | 20                           | 5                    | 9              | Multiple penetrat. duod. ulcers     |
| 375     | 38                 | 5                    | 20                           | 5                    | 5½             | Negative G. I. T.                   |

\* Died in hyperthermia (rectal temperature above 108°F).

No. of dogs tested 15

No. of dogs with ulcer and/or erosion 11

in a good general state of nutrition, free of any infection and secreted clear pouch juice. To facilitate the collection of the gastric juice without spillage on the treadmill both pouches were made with a 30 French mushroom catheter as an outlet for the gastric juice. The test period was begun at 9:00 a. m. Routinely food pans were removed from cages at 5:00 p. m. on the day preceding the test insuring a 16-hour fasting period before each experiment. Water was allowed ad lib up to but not after the time of the onset of the experiment. The samples were collected at one-half-hour intervals. The pouches were tested alternately on and off the treadmill. Dogs tested on the treadmill were run for 20 to 30 minutes before the collection of gastric juice was begun. All samples were analyzed the same day for volume, free and total acid, and pH, volume permitting.

In order to test the depressant action of muscular fatigue on gastric secretion an artificially produced stimulation of pouch secretion was created using one-half milligram histamine-base (1.37 mg histamine phosphate) injected subcutaneously. All dogs were given one or more days rest between experiments. Diet consisted of horsemeat, milk, and dog biscuits fed at approximately the same time each day.

Exp. I. *Results.* The incidence of hista-

amine-in-beeswax provoked ulcer or erosion gastric and/or duodenal) following strenuous muscular exercise is shown in Table I. This incidence is to be compared with the results as shown in Table II of injection of the same dose of histamine-in-beeswax for a comparable length of time without the effect of fatigue. Of the 2 dogs which were run on the treadmill as outlined above but were not given histamine-in-beeswax injections neither developed ulcers or erosions. However, at autopsy one of these animals (No. 326) showed a remarkably severe duodenitis. The duodenum was fiery red in color due to submucosal hemorrhages from the pylorus to the point of attachment of the ligament of Treitz. Microscopically sections from this area showed intense dilatation of the capillaries within the mucosa with extravasation of red blood cells. The colon likewise showed a rather severe colitis, the mucosal surface being bright red in color due to congestion and submucosal hemorrhages. This appearance of the colon was quite a common finding at autopsy also in the dogs run on the treadmill and given histamine. (Table I).

The blood changes caused by this amount of exercise on the treadmill were a mild hemoconcentration, a moderate fall in blood sugar immediately following exercise, and a polymorphonuclear leucocytosis above 25,000

TABLE II.  
Production of Ulcer in Normal Dogs.  
(30 mg histamine-base in Beeswax daily.)  
Control Series—No Muscular Fatigue.

| Dog No.                                | Initial wt, lbs | No. of hist. inj. | Wt, loss lbs. | Results                         |
|----------------------------------------|-----------------|-------------------|---------------|---------------------------------|
| 960                                    | 40              | 6                 | 4             | Negative gastrointestinal tract |
| 980                                    | 31              | 5                 | —             | " " "                           |
| 993                                    | 35              | 5                 | 1             | Single duodenal erosion         |
| 5                                      | 37              | 5                 | 2½            | Negative gastrointestinal tract |
| 11                                     | 47              | 5                 | 4             | " " "                           |
| 52                                     | 22              | 5                 | 2½            | " " "                           |
| 65                                     | 32              | 5                 | 4             | Duodenal ulcer                  |
| 380                                    | 30              | 6                 | 4½            | Negative gastrointestinal tract |
| 282                                    | 23              | 5                 | 3¾            | " " "                           |
| 870                                    | 17              | 6                 | 0             | " " "                           |
| 996                                    | 15              | 5                 | 0             | " " "                           |
| 12                                     | 18              | 5                 | 2             | Single duodenal erosion         |
| 51                                     | 21              | 5                 | 1½            | Negative gastrointestinal tract |
| No. of dogs injected                   |                 |                   | 13            |                                 |
| No. of dogs with ulcer and/or erosions |                 |                   | 3             |                                 |

TABLE III.  
Effect of Muscular Fatigue on Gastric Pouch Secretion.  
Average Values.\*

| Dog No. |         | Fasting Vol., cc | Free acid                 | 1st ½ hr after histamine† |                    | 2nd ½ hr after histamine |                    | 3rd ½ hr after histamine |                    |
|---------|---------|------------------|---------------------------|---------------------------|--------------------|--------------------------|--------------------|--------------------------|--------------------|
|         |         |                  |                           | HCl Vol. cc               | HCl output mg/½ hr | HCl Vol. cc              | HCl output mg/½ hr | HCl Vol. cc              | HCl output mg/½ hr |
| 689     | Resting | 2.26             | Absent 4 out of 9 trials  | 9.22                      | 44.75              | 5.38                     | 27.97              | 0.58                     | qns.               |
|         | Fatigue | 0.21             | Absent 7 out of 10 trials | 3.79                      | 16.90              | 4.13                     | 20.31              | 0.35                     | qns.               |
| 21      | Resting | 0.37             | Absent 1 out of 6 trials  | 8.20                      | 37.26              | 15.43                    | 89.11              | 3.31                     | 18.55              |
|         | Fatigue | 0.09             | Absent 3 out of 5 trials  | 7.10                      | 33.69              | 8.30                     | 47.10              | 1.26                     | 5.72               |

\* Dog 689 tested 19 times.

Dog 21 tested 11 times.

† Dose of histamine phosphate 1.37 mg aqueous solution subcut.

which persists as long as 24 hours after the termination of a 4-hour period on the treadmill.

All dogs on the treadmill showed an elevation of rectal temperature which was roughly correlated with the amount of fatigue and their physical condition. The average elevation was 2° F.

Exp. II. *Results.* Studies of the effects of muscular fatigue on gastric secretion are summarized in Table III. Both dogs show a depression of volume and free acidity of the fasting (basal) pouch secretion. Moreover, the basal pouch secretion was noticeably more mucoid (often jelling in the bottom of the tube) when the animal was fatigued. Upon the background of an artificially introduced stimulus to gastric secretion in the form of

an injection of aqueous histamine the depressant effect of muscular fatigue becomes much more apparent upon the volume of gastric juice. After aqueous histamine stimulation in exercised animals there is also a consistent, but small, reduction in degrees of free and total acid in the pouch juice. However, the main depressant effect on the production of total hydrochloric acid in muscular fatigued animals is the reduction in volume of juice secreted. The results in Table III are reported in terms of weight or output of hydrochloric acid per unit time which is the most reliable criterion of the rate of acid secretion in the stomach. (Lim).<sup>2</sup>

*Discussion.* These results indicate that mod-

<sup>2</sup> Lim, R. K. S., *Am. J. Physiol.*, 1924, **69**, 318.



FIG. 1.

Stomach from dog No. 7, dying with a perforated duodenal ulcer after being run a total of eleven hours on the treadmill over a three-day period and at the same time receiving a daily injection of histamine-base.

erately severe muscular fatigue abets the histamine-provoked ulcer quite appreciably while at the same time depressing the output of hydrochloric acid. These seemingly paradoxical findings would suggest that the ulcer abetting effect of muscular fatigue is an effect on the mucosa itself (most probably on its blood supply) which renders it more vulnerable to the digestive action of the acid-pepsin mixture. There seems little reason to doubt that strenuous muscular exercise would cause a disturbance in the blood flow through the gastrointestinal tract by partitioning available blood volume in favor of the skeletal muscles. Evidence from this laboratory has shown that vasoconstriction<sup>3</sup> produced by adrenalin-in-beeswax injection or by liberation of adrenalin due to exposure to cold<sup>4</sup> may aid and abet the ulcer diathesis by creating such anoxic areas that fail to resist the digestive action of gastric juice. Muscular fatigue<sup>5</sup> is likewise known to cause the liberation of adrenalin.

The greater weight loss in the experimental group (Table I) was due in part to the muscular exertion and in part due to the earlier development of an ulcer with consequent anorexia.

The hyperthermia associated with muscular fatigue may be a factor in the suppression of gastric secretion observed.

*Conclusions.* 1. Muscular fatigue in dogs abets the occurrence of the ulcer produced by chronic histamine stimulation.

2. Muscular fatigue in the dog depresses the output of hydrochloric acid in gastric juice from Heidenhain pouches both under basal conditions and after an artificial stimulation (aqueous histamine) due principally to a reduction in the volume of juice secreted.

<sup>3</sup> Baronofsky, I., and Wangensteen, O. H., *Bull. Am. Coll. Surg.*, 1945, **30**, 59.

<sup>4</sup> Lillehei, C. W., unpublished data.

<sup>5</sup> Gellhorn, E., *Autonomic Nervous Regulations*, Interscience Publishers, Inc., New York, N. Y., 1943, p. 135.