

ed with unfiltered sputums treated with penicillin and streptomycin singly and in combination. The combination of agents proved to be more effective than either one alone in preventing bacterial contamination and

permitting survival of the embryos. Contaminations with Gram-negative bacilli which were resistant to the action of penicillin were controlled in many instances by the addition of streptomycin.

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Role of Nitroglycerin in Accelerating Occurrence of the Histamine- Provoked Ulcer.*

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The importance of the vascular factor in the ulcer diathesis has been recently re-emphasized. Relative anemia of the mucous membrane of the esophagus, stomach, or duodenum of various experimental animals produced by adrenaline-in-beeswax,¹ fat emboli,² and portal hypertension,³ has been shown to render these structures much more susceptible to histamine-provoked ulcer and/or erosion. In other words, even temporary areas of anemia in the esophageal, gastric or duodenal walls render those areas prone to injury by the gastric juice. The purpose of this presentation is to indicate our observations on the acceleration of the histamine-provoked ulcer in rabbits and dogs, by a drug, nitroglycerin, which dilates the smaller splanchnic vessels.⁴

Methods. These experiments were carried

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¹ Baronofsky, I., and Wangenstein, O. H., *Bull. Am. Coll. Surg.*, 1945, **30**, 59.

² Baronofsky, I., Merendino, K. A., Bratrud, J. E., and Wangenstein, O. H., *PROC. SOC. EXP. BIOL. AND MED.*, 1945, **59**, 231.

³ Baronofsky, I., and Wangenstein, O. H., *PROC. SOC. EXP. BIOL. AND MED.*, 1945, **59**, 234.

⁴ Goodman, L., and Gilman, A., *The Pharmacological Basis of Therapeutics*, pp. 550, MacMillan, New York, 1941.

out on rabbits and dogs in 4 series. In the first series, which consisted of rabbits, 0.97 mg nitroglycerin, embedded in beeswax, was implanted daily in the back muscles, in addition to 30 mg of the histamine-in-beeswax mixture prepared after the method of Code and Varco.⁵ The animals were sacrificed after varying periods of time. In the second series, dogs were used. Some of these animals received 1.95 mg nitroglycerin embedded in beeswax daily, in addition to 30 mg histamine-in-beeswax intramuscularly each evening. To the remainder of the dogs 30 mg histamine-in-beeswax alone was administered each evening. In each instance the dogs' feed pans were removed and no more food given until the following morning. All the dogs were sacrificed within 2 to 6 days after the beginning of the administration of histamine.

In the third series, the effect of an aqueous solution of 1.3 mg nitroglycerin injected subcutaneously was studied upon dogs with Pavlov and Heidenhain pouches.

In the fourth series recordings of blood pressures were made on anesthetized dogs while the stomach mucosa was exposed and observed for any changes after injection of aqueous nitroglycerin 1.3 mg intramuscularly and intravenously. One series of blood pressure recordings on one animal was recorded on a kymogram by cannulation of a carotid artery. In the other animal used, the blood pressure was measured by femoral artery puncture, by

⁵ Code, C. F., and Varco, R. L., *PROC. SOC. EXP. BIOL. AND MED.*, 1940, **44**, 475.

TABLE I.
Production of Uleer in Rabbits with Both Nitroglycerin and Histamine-in-Beeswax.

Rabbit No.	Daily dose of nitroglycerin in beeswax mg	Daily dose of histamine base mg	Number of injections	Results
1	.97	30	1	Retroperitoneal hematoma probably from rupturing vessel during injection of histamine. Two bleeding points distal to pylorus
2	.97	30	7	Bleeding duodenal ulcers and 1 perforated duodenal ulcer
3	.97	30	9	Bleeding antral ulcer
4	.97	30	4	Perforating and bleeding duodenal ulcer
5	.97	30	4	Bleeding duodenal ulcer
6	.97	30	11	No ulcer
7	.97	30	2	"
8	.97	30	2	Perforating antral ulcer
9	.97	30	2	"
10	.97	30	25	Uleer at junction of esophagus and stomach
11	.97	30	26	No ulcer
12	.97	30	26	Antral ulcer

Summary:

Nine out of 12 animals developed ulcers

Controls

A	.97	0	25	No ulcers
B	.97	0	25	"
C	.97	0	25	"
1 H	0	20	31	"
2 H	0	20	31	"
3 H	0	20	31	"

TABLE II.
Production of Uleer in Dogs with Both Nitroglycerin and Histamine-in-Beeswax.

Dog No.	wt lb	Daily dose of nitroglycerin in beeswax mg	Daily dose of histamine base mg	No. of injections	Results	No. of days before sacrifice
1	17	1.95	30	2	Large perforating duodenal ulcer; multiple bleeding erosions in antrum; antral ulcers	3
2	12	1.95	30	3	Multiple bleeding antral ulcers	4
3	23	1.95	30	6	Duodenal ulcer	7
4	15	1.95	30	4	Perforating duodenal ulcer; cardio-esophageal ulcer	5
Controls						
5	47	0	30	3	No ulcer	4
6	24	0	30	6	"	7
7	52	0	30	6	"	7

Summary:

Dogs receiving both nitroglycerin and histamine—% with ulcers—100%
Dogs receiving no nitroglycerin but histamine—% with ulcers—0%

use of a mercury manometer.

Experiments. Series I. Twelve rabbits were used in this series. Both the nitroglycerin and histamine were administered for periods varying from one to 26 days.

Series II. Seven dogs were used in this series. Four dogs received both nitroglycerin

and histamine for periods varying from 2 to 6 days. The 3 remaining dogs were given histamine alone for periods of 3 to 6 days.

Series III. Aqueous nitroglycerin was injected subcutaneously into the Pavlov pouch and Heidenhain pouch dog. Collections were then taken and gastric analyses for volume

and free and total HCl were made.

Series IV. Two dogs were used in this series and aqueous nitroglycerin was injected intramuscularly and in one instance intravenously. If the blood pressure showed no change within 15 minutes, another dose was given. This was repeated for a total of 3 doses intramuscularly and one intravenous dose in one dog and 3 doses intramuscularly in the other.

Results. The results of Series I are tabulated in Table I. Nine out of 12 rabbits receiving both nitroglycerin and histamine had ulcers and/or erosions. There were no ulcers in the control animals.

Table II represents the results in Series II. In the dogs receiving both nitroglycerin and histamine-in-beeswax, ulcers were observed in an equal period of time as in animals receiving histamine-in-beeswax alone.

In the gastric secretion studies (Series III) no stimulation of either free HCL or volume by aqueous nitroglycerin was observed. Three readings on the Pavlov pouch dog and 3 on the Heidenhain pouch dog were made.

The studies on blood pressure revealed no significant findings. However, the changes in the exposed gastric mucosa were certainly significant. After the initial dose of nitroglycerin a definite blanching of circular areas of mucosa took place. This occurred within 2 minutes after the drug had been given. As time went on, this blanching became even more marked. This marked pallor lasted during the entire experiment.

Comment. It is apparent from these experiments that nitroglycerin-in-beeswax aids and abets the ulcer diathesis. It has been shown that the primary action of the nitrites is on the venous side of the circulation. There is a decreased venous tone in both the splanchnic and peripheral areas. The vasomotor responses of the arterioles to certain local and reflex stimuli are maintained in the presence

of decreased venous tone.⁶ It has also been shown that vascular changes observed as variations in color of the exposed gastric mucous membrane actually reflect changes in blood flow.⁷ The blanching of the gastric mucosa is thus an indication of decreased blood flow. This occurrence, coupled with venous pooling, may result in such a low blood flow to the mucosa that a dangerous degree of anoxemia is produced, which condition, if maintained over a long period of time, increases the ulcer diathesis. We have been unable to produce ulcer in rabbits, with histamine alone.⁸ However, as is indicated herein, bleeding ulcers and erosions follow regularly when histamine administration is accompanied by implantation of nitroglycerin-in-beeswax.

The uniform production of ulcer in dogs within 2 to 6 days following a daily injection of both nitroglycerin and histamine emphasizes the importance of the vascular factor in the ulcer diathesis.

Summary. Nitroglycerin - in - beeswax is shown to aid and abet the histamine-provoked ulcer in dogs and rabbits. The effect of nitroglycerin is believed to be due to its venous pooling property; and this action, coupled with normal arteriolar reflex contractile responses, leads, after prolonged administration, to resultant areas of impaired circulation in the mucous membrane of the esophagus, stomach and duodenum. These areas of lowered resistance are then subjected to acid-peptic digestion with resultant ulcer and/or erosion formation.

⁶ Watkins, R. W., Haynes, F. W., and Weiss, S., *J. Clin. Invest.*, 1937, **16**, 85.

⁷ Wolf, S., and Wolff, H. G., *Human Gastric Function*, pp. 49, Oxford University, New York, 1943.

⁸ Hay, L. J., Varco, R. L., Code, C. F., and Wangenstein, O. H., *Surg. Gyn. and Obst.*, 1942, **75**, 170.