wise are cured by intramuscular streptomycin alone. The intracerebral pasteurella infection of mice is strictly of the "test-tube" type and treatment is successful only if started prior to the appearance of symptoms.

Mice infected with the same pasteurella by the "natural" respiratory route suffer from a slower, progressive disease and die usually from anoxia due to widespread pneumonic lesions. Streptomycin is effective when started relatively late in that disease process, but even high doses may cure only a certain proportion of the animals. Such late treatment emphasized differences between dosage schedules, not apparent under less critical conditions. The use of similar "natural" types of infection in chemotherapeutic testing is not likely to yield as clear-cut pharmacological results as the "test-tube" types but it might contribute information on the dynamics of antibiotic action important in human disease.

Summary. 1. The therapeutic effect of streptomycin was evaluated in mice infected with a pneumotropic pasteurella either by the respiratory or by the intracerebral route.

2. When treatment was started within 4 hours after infection intracerebrally mice could be saved by streptomycin injected subcutaneously. With a total dose of 0.3 g/kg streptomycin the main factor determining success of therapy was the time interval between infection and first administration of antibiotic.

3. With comparable dosage regimens larger amounts of streptomycin were necessary to cure the intracerebral than the respiratory infection.

4. When treatment of the pulmonary infection was delayed for 18 hours, until symptoms and lesions were present, marked differences appeared in the effectiveness of dosage schedules similar in their effects when treatment was started soon after infection.

5. The possible usefulness of "natural" type infections in chemotherapeutic experiments is discussed and compared to the "test-tube" type of experimental disease.

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Failure of an Extract of Pregnant Mares' Urine to Influence Gastric Secretion in Man.

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The effect of extracts of urine upon gastric secretion and upon the course of experimentally induced ulcer has been studied by many investigators. Sandweiss, Saltzstein, and Farbman[1,2] noted delay or prevention of ulcers in the dog following the administration of extracts prepared from human pregnancy urine and the urine from normal women. Various observers[3-9] have reported the presence in human and canine urine of a substance inhibiting gastric motility and the secretion stimulated by histamine and by a meal. Fur-

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8 Culmer, C. U., Gray, J. S., Adkinson, J. L., and Ivy, A. C., *Science*, 1940, **91**, 147.

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TABLE I.
Effect of Extract of Pregnant Mares' Urine (Kutrol) on Nocturnal Gastric Secretion of Patients with Peptic Ulcer.

		Control period				After period		
	Case	Vol. (cc)	Free HCl (Cl units)	Total output HCl (mg)	Amt Kutrol (g)	Vol. (cc)	Free HCl (Cl units)	Total output HCl (mg)
				Active Material				
C.O'K. No. 423401		585	53	1120				
♂, 43	1				1.125	590	54	1151
gastric ulcer		440	50	801				
J.D. No. 324931		619	20	440				
♂, 50	2				1.875	1048	38	1434
gastric ulcer		844	22	662				
K.A. No. 421560								
♀, 44, duod. ulcer	3	919	52	1743	1.875	953	57	1965
A.B. No. 416714								
♂, 44, duod. ulcer	4	637	18	443	1.875	526	24	470
E.D. No. 427655								
♂, 38, duod. ulcer	5	1171	64	2704	7.125	922	51	2207
J.I. No. 214008								
♂, 39, duod. ulcer	6	1326	79	3831	7.125	1252	53	2393
E.R. No. 428179								
♂, 56, duod. ulcer	7	830	68	2062	7.125	647	57	1332
S.R. No. 435305								
♂, 52, duod. ulcer	8	1124	81	3314	7.50	1273	76	3456
				Control Material				
J. McA No. 347846								
♂, 33, duod. ulcer	9	1163	47	2028	7.125	1140	48	2415
A.H. No. 432870								
♀, 56, duod. ulcer	10	918	71	2377	7.125	1262	69	3191
A.H. No. 403706								
♂, 57, duod. ulcer	11	1135	48	1965	7.125	910	53	1785
J.R. No. 232510								
♂, 57, duod. ulcer	12	1054	69	2633	7.125	1139	67	2513

ther study[10-11] resulted in a preparation, designated as urogastrone, free of pyrogenic impurities and gonadotropic hormones. When administered subcutaneously, the quantity of extract effective against the ulcers resulting from the Mann-Williamson operation appeared too small to reduce gastric secretion; the protective action, therefore, was attributed to some factor other than that inhibiting gastric secretion. Sandweiss *et al.*[12] observed beneficial effects against experimental ulcer in the presence of an essentially unaltered acid gastric juice; the protective agent was found in the urine of pregnant and of normal females, but only in small quantities in the urine of patients with peptic ulcer.

The latest preparation to receive attention is an extract of the urine from pregnant mares, termed Kutrol. This material is described[13] as entirely devoid of estrogenic or gonadotropic activity, highly soluble in water, and

[10] Gray, J. S., Culmer, C. U., Wieczorowski, E., and Adkinson, J. L., PROC. SOC. EXP. BIOL. AND MED., 1940, **43**, 225.

[11] Gray, J. S., Wieczorowski, E., and Ivy, A. C., *Am. J. Dig. Dis.*, 1940, **7**, 513.

[12] Sandweiss, D. J., Sugarman, M. H., Friedman, M. H. F., Saltzstein, H. C., and Farbman, A. A., *Am. J. Dig. Dis.*, 1941, **8**, 371.

[13] Sharp, E. A., Personal communication.

manifesting an acceptable degree of antiulcer activity when assayed on the Shay rat; its precise nature is, however, not known. Bercovitz, Page, and Heffner[14] recently have reported encouraging results in the treatment of chronic duodenal ulcer with doses of 0.6 g by mouth daily in divided amounts. It appeared desirable, therefore, to determine the effect of Kutrol upon gastric secretion in man.

Method of Study. The method of investigation was similar to that described previously.[15,16] Twelve patients, 10 with active duodenal ulcer and 2 with gastric ulcer, were studied. Continuous gastric suction was maintained by a Gomco aspirator, the containers being replaced each hour. In 4 patients the 12-hour nocturnal gastric secretion was measured before and approximately 2 hours after the administration of the extract* via the stomach tube; one individual received 0.225 g every 2 hours for 5 doses, a total of 1.125 g; the remaining 3 were given 1.875 g in divided amounts. The subjects were maintained on a liquid diet during the interval when aspiration was discontinued.

In 4 patients gastric suction was continued for 36 hours. After 16 or 17 hours (either at 1:30 or 2:30 p.m.) 7.125 to 7.50 g of Kutrol were introduced into the stomach via the Levine tube. Aspiration was resumed after an interval of 3 hours, and maintained for an additional 16 or 17 hours. The remaining 4 patients were studied in an identical manner but received 7.50 g of an "inactive" material; this group, therefore, served as an additional control. Fluid and electrolyte balance was maintained in the two latter groups by the intravenous administration of 5% glucose in isotonic saline solution.

[14] Bercovitz, Z. T., Page, R. C., and Heffner, R. R., Am. Gastroenterological Assn., May 1, 1948, Atlantic City, N. J.

[15] Levin, E., Kirsner, J. B., Palmer, W. L., and Butler, C., *Arch. Surg.*, 1948, **46**, 345.

[16] Kirsner, J. B., Levin, E., and Palmer, W. L., PROC. SOC. EXP. BIOL. AND MED., 1948, **68**, 90.

* Made available through the kindness of Drs. Z. Bercovitz and E. A. Sharp. The extract was prepared in kapseals, each containing 0.075 g of the active material in the form of a powder.

Results. The data for the 12-hour nocturnal gastric secretion are summarized in Table I. The volume, free acidity and output of hydrochloric acid were not significantly reduced despite the administration of 7.50 g of the extract of pregnant mares' urine, a quantity 12 times larger than the present clinical dose. The control material likewise was without discernible effect. The administration of Kutrol did not decrease the con-

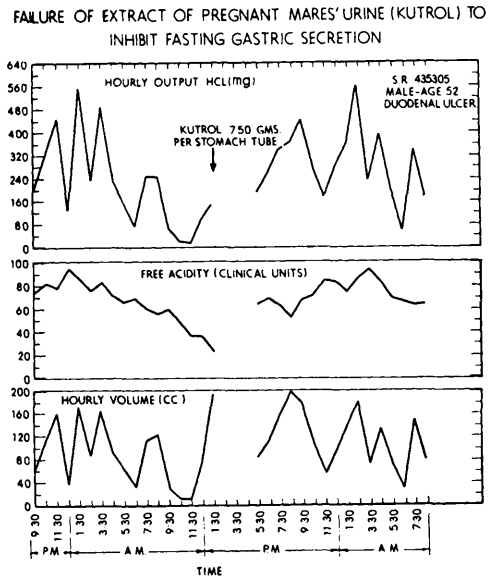

FIG. 1.

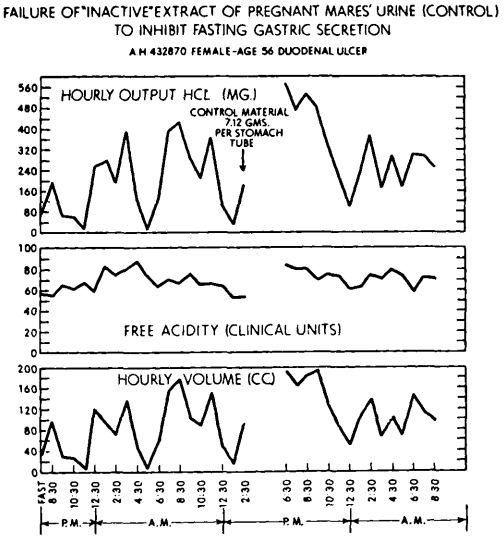

FIG. 2.

tinuous, fasting, 36-hour secretion; representative studies with the active extract and the control material are shown in Fig. 1 and 2. The hourly volume, free acidity, and output of hydrochloric acid remained essentially unchanged. No untoward effects were observed in these studies.

Conclusion. The intragastric administration of an extract of pregnant mares' urine, Kutrol, in quantities as large as 7.50 g does not decrease the volume, free acidity, or output of hydrochloric acid in the 12-hour nocturnal gastric secretion or in the continuous 36-hour secretion of patients with peptic ulcer.

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Effect of Forced Expiration upon Finger and Pulse Volume.*

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Although there is general agreement about the peripheral arteriolar constrictive effect of a deep inspiration, the effect of a deep expiration upon peripheral circulation is not yet clarified. Bolton, Carmichael, and Sturup[1] and Gilliat[2] report no effect on finger volume, whereas Uhlenbruck[3] and de Lalla[4] observed a diminution of finger volume, and the latter reported coincident decrease in skin temperature and arterial rate of flow following a forced expiration. Therefore it seemed of interest to study further the possible changes in finger and pulse volume incident to a deep expiration.

Method. Pulse and finger volumes were recorded in two ways using a finger plethysmograph each time: (1) In 11 cases the plethysmograph changes were picked up by a piezo-electric crystal whose output was fed into an amplifier-galvanometer recording system. The deflections of the mirror galvanometer were recorded on film moving at 25 mm per second; in 4 of these tracings a simultaneous ballistocardiogram was recorded. With this method any desired amplification of the pulse volume could be obtained, but the total finger volume changes could not be recorded since the system would not maintain a change of baseline; (2) In 5 cases the output of the plethysmograph was put directly into a Frank capsule whose mirror deflections were recorded in the same manner as above. Although the pulse impulse waves were not large in amplitude with this technic, the total finger volume changes were accurately recorded. Respirations were recorded simultaneously in all cases by a pneumograph-Frank capsule arrangement.

Six normal adult subjects were used, 4 males and 2 females, and a total of 16 records were obtained. They were instructed in the following manner: "At no time take a deep inspiration; at the end of a normal inspiration expire forcefully and rapidly, as much as you can, through your mouth; do not hold your breath, but continue to breathe normally directly afterwards." This maneuver is described in detail since the manner of performance seems to be important.

Results. In all cases there was an immediate decrease in pulse volume, and in the 5 tracings recorded with the Frank capsule there was a simultaneous fall in total finger

* This work was carried out under a contract between the Office of Naval Research and the University of Rochester, School of Medicine and Dentistry.

1 Bolton, B., Carmichael, E. A., and Sturup, G., *J. Phys.*, 1946, **86**, 83.

2 Gilliatt, R. W., *J. Physiol.*, 1948, **107**, 76.

3 Uhlenbruck, P., *Z. Biol.*, 1924, **80**, 317.

4 de Lalla, V., *Am. J. Physiol.*, 1948, **152**, 122.