tained when the blood glucose concentration was further raised. The whole surplus of glucose was rejected in the urine, presenting also during work the phenomena of overflow diabetes described for resting animals.[2] If 2500-3000 mg% of blood glucose were reached some extra amount of work was imposed upon the muscles by convulsive phenomena originating from stimulation of the segmental, motor nuclei across the whole neuraxis[11] and seemed to give some transitory further increase of glucose retention, before final weakness and failure of circulation took place.

Up to 1000 mg% of blood glucose, blood lactate was somewhat higher at work than at rest. At 1000 mg% a peak of lactate concentration was reached (35 mg% above basal value) almost exactly equal to the one observed for a resting animal. This concentration persisted up to 2500 mg% of blood glucose, when convulsive phenomena began to augment the blood lactate formation intensely. In the urine at each value of blood glucose, lactate excretion was greater at work than at rest, the peak being reached at 1600 mg% of blood glucose; then the elimination decreased both at work and at rest with deterioration of circulation in the kidneys. It is evident that each value of blood glucose at work corresponded to a higher level of glucose transformation than at rest. Therefore, as expected, lactate, the rejection of which into the blood stream parallels glucose transformation, is formed in larger amounts during work at identical blood glucose levels, than at rest. The work itself also may contribute to its increased passage into the bloodstream.

Conclusion. Work does not increase to an unlimited extent the transformation of glucose supplied to the muscles in highest amounts. Its utilization at work, although even almost doubled, is governed by laws similar to those at rest.

11 Wierzuchowski, M., Toczyski, T., and Sysa, J., *Am. J. Med. Sc.*, 1948, **215**, 108.

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Stimulation of Gastric Secretion by Urticariogenic Wetting Agent (Tween 20) and Its Inhibition by Benadryl.

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The synthetic wetting agent Tween 20 (Atlas Powder Co.), which is a polyoxyalkylene derivative of sorbitan monolaurate, has recently been shown to be capable of producing generalized urticaria when injected intravenously in dogs.[1]

Several investigators[2,3] have found that when whealing of the skin is produced by mechanical or thermal injury in the human, gastric acid secretion is stimulated. The usual interpretation of this phenomenon is that injury to the skin causes the epidermal cells to release either histamine or a histamine-like substance (H-substance). This substance acts locally at the site of release to produce the whealing reaction and some of it is carried into the general circulation where it produces systemic effects similar to those produced by the injection of histamine, including stimulation of acid secretion by the stomach.

The present study was undertaken in order to determine whether the urticaria which occurs in dogs when Tween 20 is injected is accompanied by stimulation of gastric se-

1 Ivy, A. C., Tanturi, C.A., Hernandez, R., and Baroso, E., *Arch. Derm.*, in press.

2 Horton, B. T., Brown, G. E., and Roth, G. M., *J.A.M.A.*, 1936, **107**, 1263.

3 Kalk, H., *Klin. Wschr.*, 1929, **8**, 64.

TABLE I.

The Effect of Tween 20 (0.8 mg/kg Intravenously) on Gastric Secretion and Urticarial Reaction in Dogs, With and Without Benadryl (10 mg/kg Intravenously) One-half Hour Before the Tween 20.

	Tween 20 without Benadryl					Tween 20 after Benadryl				
	Urticaria			Basal secretion Free HCl output	Gastric secretion Free HCl output	Urticaria			Basal secretion Free HCl output	Gastric secretion Free HCl output
Dog No.	++	+	0	(mg/hr)	(mg/2 hr)	++	+	0	(mg/hr)	(mg/2 hr)
1	x			0	58.8		x		0	12.1
1	x			1.9	130.9		x		0	6.2
2	x			0	6.9			x	0.2	0
2	x			0	9.4			x	0	0
2	x			0	25.6			x	0	0
3	x			0.8	37.2		x		0	6.5
3	x			0	19.6		x		0	0
4	x			0	18.1		x		1.8	34.0
4	x			0	14.2	x			0	58.3
5	x			2.1	71.0		x		0	0
5	x			0	14.9			x	0	0
6	x			0	19.6			x	0	6.4
6	x			0	92.7		x		2.0	16.3
6	x			0.6	32.4			x	0	14.5
7	x			0	31.0		x		0	5.5
7	x			0	15.7		x		0	24.9
8	x			0.9	25.8			x	0.4	8.3
8	x			0	16.9	x			0	35.8
Total or avg	18	0	0	0.4	35.5	2	9	7	0.3	12.7

++ Marked urticarial response.
\+ Slight " "
0 No " "

Statistical analysis (method of paired comparison, Snedecor,[5] p. 84): mean difference = 22.8, standard error of mean difference = ± 10, t = 2.29, p ± 0.04.

cretion. Since we found that gastric secretion was stimulated, we proceeded to study the effect of the antihistaminic drug benadryl (beta-dimethylaminoethyl benzhydryl ether hydrochloride) on this stimulation.

Procedure. Eight dogs with pouches of the entire stomach were used. Tween 20 was injected intravenously in a dose of 0.8 mg per kilo of body weight, using a 1% aqueous solution. In one half of the experiments, a 1% aqueous solution of benadryl was injected intravenously in a dose of 10 mg per kilo one half hour before giving the Tween 20. Gastric juice was collected every half hour for 2 periods preceding the injection of Tween 20 and for 4 periods after the injection. The volume of each sample was measured and it was then titrated with 0.027 N NaOH, using *p*-dimethylaminoazobenzene as an indicator. Observations were made on the severity of the urticarial reaction in each instance. Dogs were not used oftener than once every 5 days for these experiments.

Results. The results are summarized in Table I. Tween 20 alone produced marked urticaria and stimulated gastric secretion in each of the 18 tests on the 8 dogs. The gastric secretory response begins in 15 to 45 minutes following the injection, reaches its peak during the second half-hour period, and has returned to the basal level by the end of 2 hours. Urticaria begins to occur 3 to 5 minutes after the injection, reaches a maximum in 10 to 15 minutes, and has usually subsided completely within 30 minutes after injection. When Tween 20 was injected one-half hour after benadryl had been given, both urticaria and gastric secretion were either completely abolished or definitely diminished in 14 out of 18 tests on 7 of the dogs. In the remaining 4 tests on 3 dogs, urticaria was only questionably or moderately reduced and gastric secretion was the same or slightly greater than in the tests

[5] Snedecor, G. W., *Statistical Methods*, 4th ed., Iowa State College Press, Ames, Iowa, 1946.

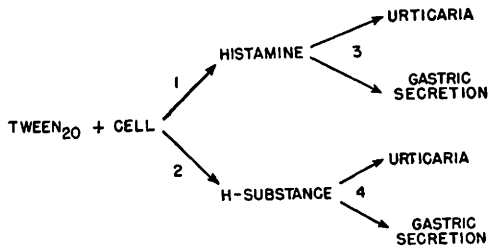

FIG. 1.

with Tween 20 alone. Statistical analysis reveals that the difference between the results with and without benadryl could be expected to occur by chance variation due to random sampling error in less than 4 out of 100 similar experiments.

Discussion. The simplest explanation that could be offered for the results we have obtained is that Tween 20 causes histamine to be released and that benadryl counteracts both the urticariogenic and gastric secretory effects of the released histamine. However, we[4] have previously shown that benadryl does not inhibit the gastric secretory response to histamine in dogs. Inasmuch as a dose of benadryl of only 5 mg/kg subcutaneously was used in these earlier studies, we have repeated the experiment using 10 mg/kg intravenously. In 4 tests on 4 dogs, this higher dose of benadryl also failed to depress the secretory response to 0.0125 mg of histamine dihydrochloride given every 10 minutes. The average secretory response when this dose of histamine is used is comparable to the average secretory response to the dose of Tween 20 used in these studies. Therefore, inasmuch as benadryl does not counteract the action of histamine on the gastric glands, another explanation must be sought for the depression of the secretion evoked by Tween 20.

Fig. 1 is a simple schematic representation of some of the possible mechanisms by which Tween 20 may act and the points at which benadryl may counteract it. According to this analysis, if Tween 20 releases histamine, then benadryl must act at 1 to prevent the release of this histamine. This is so because once the histamine is released, benadryl cannot counteract its action on gastric secretion; that is, it cannot act at the point designated 3 in the diagram. On the other hand, if the gastric secretion produced by Tween 20 is due to a histamine-like substance, then benadryl may either block its formation or block its action on the gastric glands (points 2 or 4 in the diagram).

In any case, it is significant that the action of benadryl in counteracting gastric secretion stimulated by Tween 20 cannot be accounted for on the basis of its known pharmacological properties. This suggests that benadryl may inhibit anaphylactic and anaphylactoid reactions by some mechanism in addition to blocking the action of histamine on effector cells.

Summary. 1. Tween 20 produces urticaria and stimulates gastric secretion when injected intravenously in a dose of 0.8 mg/kg in dogs with gastric pouches.

2. Pretreatment with benadryl (10 mg/kg intravenously) prevents or reduces the urticariogenic and secretory effects of Tween 20 in most instances.

3. Inasmuch as benadryl does not inhibit histamine-stimulated gastric secretion, the mode of action of benadryl in counteracting Tween 20 stimulated secretion must involve another mechanism.

[4] Sangster, W., Grossman, M. I., and Ivy, A. C., *Gastroenterology*, 1946, **6**, 436.