muscular injections of 100 mg of cortisone daily. At the end of 4 days of treatment there was definite improvement. The treatment was continued for 3 more days making a total of 7 days. Two days after treatment was discontinued the symptoms began to return. Six days later the animal was unable to rise without assistance. After the animal had gone 31 days without treatment and had not shown any appreciable improvement, treatment with ACTH was begun. Daily intramuscular injections of 40 mg were given for 5 days without any appreciable effect.

A second hog weighing about 200 lb was given 100 mg doses of cortisone daily for 6 days. Improvement was shown on the fourth and was quite definite on the fifth day after treatment was started. There was no well marked recurrence of symptoms in this animal during a period of 30 days after treatment was discontinued.

A third shoat and a fourth one, weighing about 80 lb each were treated daily with cortisone and ACTH, respectively, in the same doses as used in the foregoing trials. On the third day of treatment both animals showed definite improvement. The one being treated with ACTH was almost free of lameness. Improvement continued in both animals during six days of treatment. Three days after treatment was discontinued both animals showed a return of symptoms. On the fifth day after treatment was stopped, the animal which had been treated with cortisone showed more marked symptoms than at any time. Treatment of this animal with cortisone was then resumed and continued for 4 days. On the third day after treatment was resumed there was definite improvement. Nine days after this treatment was discontinued, the animal was again showing marked symptoms of stiffness and lameness. The other shoat which had been treated with ACTH was showing fairly well marked lameness and stiffness 20 days after treatment was stopped.

Summary. Diseased conditions occur in swine which bear considerable resemblance to rheumatic or rheumatoid diseases in the human. Some naturally affected swine showed definite improvement following treatment with cortisone and also with ACTH. More work needs to be done before drawing conclusions as to how closely analogous are the rheumatoid conditions in swine and in the human.

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Mechanism of Increased Susceptibility to Ergot Gangrene in Thyrotoxicosis. (17913)

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Ergot gangrene in the human is still occasionally reported(1,2), but fortunately is now rare. It is usually attributable to too frequent or prolonged administration of large doses of ergot alkaloids, but occasionally follows small doses. It has often been reported in association with thyrotoxicosis(3), puerperal sepsis(4-7) and jaundice(8-11), but almost never following the use of these alka-

1. Cleveland, F. E., and King, R. L., *Bull. Mason Clinic,* 1948, v2, 19.
2. Loe, R. H., *Northwest. Med.,* 1948, v47, 190.
3. Von Storch, T. J. C., *J. Am. Med. Assn.,* 1938, v111, 293.
4. Welkoff, A. S., and Ferguson, A. D., *Am. J. Ob. and Gyn.,* 1942, v44, 331.
5. McNalley, F. P., *Am. J. Ob. and Gyn.,* 1932, v23, 367.
6. Moir, C., *Proc. Roy. Soc. Med.,* 1935, v28, 1654.
7. Olesker, N. N., *Canad. Med. Assn. J.,* 1942, v46, 168.
8. Kenney, F. R., *New Eng. J. Med.,* 1946, v235, 35.
9. Yater, W., and Cahill, J. A., *J. Am. Med. Assn.,* 1936, v106, 1625.

TABLE I.
Influence of Alteration of Oxygen Consumption on Incidence of Ergotamine-Induced Gangrene in Rats.

Procedure	No. rats	Oxygen consumption (cc/min.) Avg	St. dev.	% change	Gangrene No.	%	p*	Significance
Propylthiouracil	16	2.12	.39	—41.3	8	50	>.20	0
Normal	26	3.61	.25	—	7	26.9	—	—
Thyroxin	15	5.43	.31	+50.4	15	100	<0.1	High

* Comparison of incidence of gangrene with normal.

loids in the treatment of migraine. This may be solely a question of the size of the dose employed for various conditions, but the impression has arisen that certain diseases predispose to ergot gangrene. Such a concept derives partial support from the observation that administration of thyroxin to rats increases the incidence of ergotamine induced gangrene(12). This observation is confirmed in the present study and evidence is presented that the effect is due to prolongation, by thyroxin, of the circulatory impairment produced by ergotamine.

Experimental. The incidence of gangrene of the tail was determined in a series of 26 normal rats weighing 140-200 g Following a single intraperitoneal injection of 12.5 mg/kg of ergotamine tartrate,* it was observed (Table I) that within 7 days, 7 or 26.9% of these animals developed gangrene of the tail. In order to determine whether thyrotoxicosis increased the incidence of gangrene, a series of 15 rats was injected intraperitoneally with 0.1 mg per day of crystalline thyroxin† for 10 days. During this period the oxygen consumption increased from 3.61 cc to 5.43 cc/min/animal, an average increase of 50.4%. Following this period the previous dose of ergotamine (12.5 mg/kg) was injected intraperitoneally.

Gangrene occurred in 100% of this group of rats, a significant increase in the incidence. All of these animals developed gangrene within 48 hours of the injection of ergotamine, whereas, only approximately 7% of normal animals which get gangrene from ergotamine do so within 48 hours(13). We can thus confirm the observation that thyrotoxicosis increases the susceptibility of the rat to ergotamine-induced gangrene and contribute the additional observation that gangrene occurs earlier in such animals. In contrast to previous observation(12), we find no increase in the lethal action of ergotamine. All of our thyrotoxic animals survived a dose of ergotamine fatal to 13.3% of normal animals.

Gangrene occurs as a result of vascular occlusion due to prolonged severe vasospasm produced by ergotamine. An increase in the incidence of ergotamine induced gangrene, as produced by thyroxin, might be due to either an increase in severity of the vascular occlusion or a decrease in the resistance of the tissues to vascular occlusion.

If the increased incidence of gangrene produced by thyroxin is due to increased tissue susceptibility to vascular occlusion on the basis of increased oxygen requirements, then a decrease in oxygen consumption should reduce the incidence of gangrene. Hence, 16 rats were given 25 mg per day by mouth of propylthiouracil for 6-8 weeks. At the end of this period the average oxygen consumption was 2.12 cc/min/animal, a decrease from normal of 41.3%. At the end of this period these animals were injected with 12.5 mg/kg of ergotamine. Eight or 50% of these animals developed gangrene and did so within

10. Gould, S. E., Rice, A. E., and Ginsberg, H. I., *J. Am. Med. Assn.*, 1936, v106, 1631.

11. Smith, L. A., and Eusterman, G. B., *Am. J. Dig. Dis.*, 1942, v9, 301.

12. Griffith, J. Q., and Comroe, B. J., *J. Pharm. Exp. Therap.*, 1940, v69, 34.

* Gynergen-Sandoz 1:1000 solution.

† Furnished us through the courtesy of Dr. K. W. Thompson of Roche-Organon.

13. Anderson, L. H., and Wells, J. A., PROC. SOC. EXP. BIOL. AND MED., 1948, v67, 53.

TABLE II.
Influence of Thyroxin on Ergotamine Induced Restriction of Bleeding Volume in Rats.

Hr after inj. of ergotamine	No. of rats		Bleeding volume					
			Normal		Thyroxin treated			
	Normal	Thyroxin treated	Avg	St. dev.	Avg	St. dev.	p*	Significance
Control	11	8	8.43	3.02	8.86	2.93	>.50	None
4	19	14	1.05	1.52	1.59	1.69	>.30	"
10	22	16	2.86	2.15	2.77	3.03	>.50	"
16	19	13	4.24	3.16	1.67	1.55	.01	High

* Comparison of bleeding volume of thyroxin-treated animals with those of controls.

7 days of injection. The incidence of gangrene in these animals (Table I) is not significantly different from that of the controls. Thus, it is assumed that the mechanism of the increased incidence of ergot gangrene produced by thyroxin is not altered tissue susceptibility on the basis of increased tissue requirement for oxygen, but an increase in the degree or duration of the vascular occlusion produced by ergotamine in the presence of thyrotoxicosis.

We have previously reported(13) that within 1 hour of the injection of gangrene producing doses of ergotamine in the rat, the tail may be amputated within 3 cm of the body with no appreciable bleeding. The amount of bleeding from the amputated tail provides a basis for the rough measurement of the degree and duration of vascular impairment produced by ergotamine in normal and thyrotoxic rats. Seventy-one normal rats were injected intraperitoneally with 30 mg/kg of pentobarbital sodium and sufficient heparin (2-3 mg) to prevent clotting of blood. At varying periods following the intraperitoneal injection of 12.5 mg/kg of ergotamine tartrate, the tails were amputated 3 cm from the base with sharp rib shears and the blood collected in graduated centrifuge tubes. Care was taken to continuously remove gross clots appearing on the amputated stump. The bleeding volume was recorded 2 hours following amputation, at which time bleeding from all animals had stopped.

The average bleeding volume in 11 normal rats (Table II) prior to the injection of ergotamine was 8.43 cc. Four hours after injection of ergotamine, the average bleeding volume in 19 rats was reduced to 1.05 cc. Eight of these animals did not bleed at all from the amputated tail in 2 hours. The average bleeding volume progressively increases with time, becoming 2.86 cc at 10 hours and 4.24 cc at 16 hours. However, at 16 hours the bleeding volume is still significantly less ($p = < 0.01$) than the pre-injection volume. It is only approximately 50% of this value. Thus, doses of ergotamine which may in a single injection cause gangrene, induce severe and prolonged spasm of the major arteries of the tail.

To test the effect of thyroxin on this vascular spasm, 51 rats were injected intraperitoneally with 0.1 mg/day of crystalline thyroxin for 10 days. They were prepared as were the control animals and the tails were amputated at the same time intervals. The average bleeding volume of the thyroxin treated animals (Table II) prior to the injection of ergotamine was 8.86 cc, not significantly different from the normal controls. Consequently, the effect of thyroxin on gangrene due to ergotamine is not due to an independent action of thyroxin on the vascular system. The average bleeding volume 4 hours after the injection of ergotamine was greatly reduced (1.59 cc), but not significantly more than the corresponding normal animals 4 hours after ergotamine injection. At its height, the ergotamine induced vasospasm is not greater in thyroxin treated than in normal animals. Hence, the potentiating effect of thyroxin would not seem to be an increase in the severity of the vasospasm. Correspondingly, the bleeding volume is not significantly different in the thyroxin treated group from that of the normal 10 hours after the injection of ergotamine. However, 16

hours after injection the average bleeding volume in the thyroxin treated animals (1.67 cc) is significantly less than that of the normal animals (4.24 cc) and is only approximately 18% of the value obtained prior to the injection of ergotamine.

It appears that the effect of thyroxin in increasing the susceptibility of the rat to ergotamine-induced gangrene of the tail is essentially one of prolongation of the vascular occlusion produced by ergotamine. Such an effect may be due to sensitization of the vascular musculature to the action of ergot as has been claimed for epinephrine(14). It would seem that such should result in an increase in the intensity as well as the duration of the effect. However, the present method may be too indelicate to detect an increase in an already severe vasospasm. Alternatively, thyroxin may interfere with the destruction and/or elimination of the ergot alkaloids, thus, prolonging without intensifying the effect.

In partial support of this latter hypothesis is the observation that 8 out of 10 rats developed gangrene following the injection of 12.5 mg/kg of ergotamine subsequent to exposure to chloroform vapor (2 hours in a concentration of 1.77 vol. %). This is a significant ($p = <0.02$) increase in the incidence of gangrene over normal and suggests that liver damage, by interfering with the elimination of ergot alkaloids, may predispose to ergot gangrene.

Summary. Thyrotoxicosis increases the incidence of ergotamine-induced gangrene of the tail of the rat. Reduction in oxygen consumption by propylthiouracil does not alter the incidence of ergot gangrene. Bleeding from the amputated tail of the rat is markedly reduced for prolonged periods by ergotamine and pre-treatment with thyroxin further prolongs the vasospasm so induced. It is assumed that thyroxin acts, not by altering the resistance of the tissues to vascular occlusion, nor by sensitizing the vascular musculature to ergotamine, but by prolonging the action of the alkaloids, possibly by interfering with their elimination or destruction.

14. Levy, R. L., *Am. J. Physiol.*, 1916, v41, 492.

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Effect of Hyperglycemic-Glycogenolytic Factor on Blood Sugar of Patients with Diabetes. (17914)

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In a previous communication(1) the clinical and experimental evidence suggesting that a hyperglycemic substance obtained from the pancreas may be an alpha cell hormone which causes an elevation of blood sugar by promoting hepatic glycogenolysis was reviewed. As stressed by Weisberg *et al.*(2) thus far it has not been proved that this material functions physiologically nor that it is a true hormone. This substance has been designated by Sutherland and his co-workers(3-5) as a hyperglycemic-glycogenolytic factor or H-G F.

If the H-G factor is an alpha cell hormone, it was believed that certain patients might exhibit evidences of increased or decreased activity of this substance as suggested by Thorogood and Zimmerman(6), McQuarrie

1. Pincus, I. J., *J. Clin. Endocrin.*, 1950, v10, 556.

2. Weisberg, H. F., Caren, R., Huddleston, B., and Levine, R., *Am. J. Physiol.*, 1949, v159, 98.

3. Sutherland, E. W., and Cori, C. F., *J. Biol. Chem.*, 1948, v172, 737.

4. Sutherland, E. W., and de Duve, C., *J. Biol. Chem.*, 1948, v175, 636.

5. Sutherland, E. W., Cori, C. F., Haynes, R., and Olsen, N. S., *J. Biol. Chem.*, 1949, v180, 825.