treated mice uniformly showed an extensive increase of the epithelial folds and gland-like processes which completely penetrated the thickened mucosa, the muscularis and frequently projected to the serosa (Fig. 2). The epithelium consisted of tall columnar cells which showed slight mitotic activity. In many ducts 2 types of cells were found, tall cells with an eosinophilic cytoplasm and cells with a clear cytoplasm. Evidence of cystic distension of the ducts, concretions or inflammatory processes were seldom found and never extensive. The lamina propria was histologically unchanged and the muscularis showed no hypertrophy, in fact, was difficult to discern in many hypertrophied ducts. The larger branches of the common duct were similarly involved but the intrahepatic ducts had not been affected.

Hypertrophy of the biliary ducts was observed in many mice of several different inbred strains (CBA, C_3H, C_{57}, JK, A) and hybrids which have received estradiol dipropionate and estradiol benzoate in oily solution in amounts ranging from 16.6 to 50 μg weekly, estrone pellets, or stilbestrol (250 μg weekly). All animals were maintained on a diet of Purina Fox Chow and water. The hyperplasias occurred most frequently and were most extensive in mice receiving treatment for the longer periods. Most mice surviving treatment over 450 days showed lesions of the biliary ducts. In one series of experiments 58 of 76 mice (F_1 hybrids of CBA $\times$ C_{57} strains) receiving 16.6 μg of estradiol benzoate had moderately to extremely enlarged biliary ducts. Only 4 animals had ducts that were grossly normal. The incidence was lower in mice of groups which did tolerate the injections for the longer periods. Untreated mice (with the exception of 2 castrated females with adrenal tumors) and mice receiving testosterone propionate or sesame oil, have not shown a hypertrophy of the biliary ducts.

12046

Pulmonary Circulation Time in Man at Low Body Temperatures.

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Through the coöperation of Dr. Temple Fay, we have had an opportunity to observe a large number of patients during a period

of hypothermia, induced in accordance with his new methods designed to establish the effects of low temperatures upon inoperable malignant growths.[1] Since little is known about the effects of this procedure upon the various functions of the human organism, we have undertaken a study of the circulation rate as affected by reduction in the temperature of man to an extent sufficient to induce artificial hibernation.

Methods. Circulation time was determined by the cyanide method.[2] The overwhelming factor in the results obtained is undoubtedly the circulation time through the lungs. Each patient was first tested at complete rest at normal temperatures. For this test basal conditions were obtained either by voluntary coöperation, if possible, otherwise by the administration of evipal intravenously or avertin by rectum in dosage sufficient to produce narcosis. This narcosis was confirmed by the patient's failure to shiver (after the circulation time test) when cooled by cracked ice applied directly on the entire body surface (except the head) or by a blanket containing coils containing mixtures which did not freeze when held at low temperatures. In either case (voluntary coöperation or anesthesia), the patient had been at rest at least 15 minutes before the test.

During the period of low environmental temperature,[1] the patients were entirely quiet when tested, anesthesia being used if necessary to bring this about. Patients who had an anesthetic as in the control period were tested with an anesthetic in the period of hypothermia and those that were quiet without anesthesia in the first were tested without it in the second. Blood pressure and pulse rate were recorded during the 2 temperature periods.

Skin temperatures were determined just above (2 cm) the antecubital space by thermocouple. Rectal temperatures were also recorded by a recording resistance thermometer.

With every injection of cyanide all the precautions mentioned by Robb and Weiss[2] were observed. Three sites of injection were used, antecubital, jugular, and femoral veins. This last was selected as the best measure of flow along an intraäbdominal vein. Injections were made rapidly (0.5 second); a 2% solution of sodium cyanide was used. Volumes employed were 0.3 to 0.6 cc (6-12 mg).

Circulation time as measured by this method is the time required for the injected cyanide to pass from the site of injection to the carotid and aortic chemoreceptors, stimulation of which by the

1 Smith, L. W., and Fay, T., *J. A. M. A.*, 1939, **113**, 653.
2 Robb, G. P., and Weiss, S., *Am. Heart J.*, 1932, **8**, 650.

drug elicits an abrupt increase in respiration, usually in depth only, sometimes in rate and depth. This time was measured graphically by a pneumograph-tambour system recording on a kymograph and checked by a stopwatch.

Results. A. Circulation Time Between an Antecubital Vein and the Aortic-carotid Chemoreceptors. In a series of 14 patients, this interval was measured at normal temperatures under basal conditions (with or without anesthesia) and again in the cold. The interval between injection of sodium cyanide into the antecubital vein and its arrival at the arterial chemoreceptors, as indicated by the respiratory reaction, was prolonged from an average of 16.6 seconds (14 determinations) at normal body temperature to an average of 23.5 seconds (14 determinations) in the cold. The controls varied from 11.5 seconds to 25.9 seconds. The values in the low temperature phase varied from 17.8 seconds to 30.8 seconds. Statistical computation reveals a correlation between extent of prolongation of circulation time and extent of reduction of rectal temperature of +0.32, which is scarcely significant. (Table I.)

B. Circulation Time Between a Jugular Vein and Aortic-carotid Chemoreceptors. This was measured in 10 patients at normal temperatures and again in the same patients exposed to low temperatures. The interval between the injection and the respiratory reaction was increased from an average of 11.3 seconds (10 determinations) at normal temperatures to an average of 15.2 seconds (10 determinations) in the cold. For the controls at normal temperatures the upper and lower limits were respectively 18.0 and 8.8

TABLE I.
Antecubital

Case No.	Prolongation in circulation time (sec)	Fall in rectal temp. (°F)
1	13.5	13.8
2	15.0	9.0
3	10.4	10.3
4	2.5	9.6
5	13.5	14.6
6	15.4	3.8
7	3.6	8.8
8	9.4	12.2
9	3.0	11.6
10	1.8	14.6
11	1.1	13.6
12	8.2	11.1
13	6.1	10.1
14	1.2	14.1
	Correlation +0.32	

TABLE II.
Jugular.

Case No.	Prolongation in circulation time (sec)	Fall in rectal temp. (°F)	Fall in skin temp. (°F)	Changes in index of peripheral venous flow* (sec)
3	3.0	10.3	4.8	— 7.4
6	2.4	3.8	6.5	—13.0
7	1.0	8.8	6.0	— 2.6
8	0.8	12.2	14.5	— 8.6
9	0.3	11.6	9.0	— 2.7
10	2.8	14.6	10.0	+ 1.0
11	10.4	13.6	8.0	+ 9.3
12	6.5	11.1	5.0	— 1.1
13	1.9	10.1	4.0	— 4.2
14	5.2	14.1	3.0	+ 4.0
	Correlation +0.31		Correlation —0.20	

*Prolongation —; Decrease +.

seconds, for the cold 21.6 and 9.1 seconds. Here again there was little or no correlation between the extent to which circulation time was prolonged and the amount of reduction in rectal temperature (+.31, statistical computation, Table II). The jugular vein to arterial chemoreceptor time represents what Robb and Weiss have termed the crude pulmonary circulation time.[2] It is evident that although this interval is prolonged by cold, the indicated slowing in the pulmonary circulation is not proportional to the amount of cooling.

In 10 of these patients the index of peripheral venous velocity (antecubital to chemoreceptor minus jugular to chemoreceptor time) was determined. This measured the approximate velocity of venous blood flow in the arm. Here the magnitude of the change in circulation rate was not correlated with the extent of reduction in skin temperature (statistical computation). The relationship varied from 1.3 seconds *shortening* to 2.0 seconds *prolongation* per degree Fahrenheit reduction in skin temperature. (Correlation was –.20, Table II.)

C. Circulation Time Between a Femoral Vein and Carotid-aortic Chemoreceptors. The same methods in 10 patients as in A and B gave an increase (prolongation) in the average circulation time from 11.7 seconds (10 determinations) in the normal controls to 17.4 seconds (10 determinations) in the same cases exposed to low temperatures. Here, however, there was a statistically significant correlation (+0.81) between the amount of reduction in rectal temperature and the extent of the increase in circulation time (Table III).

TABLE III.
Femoral.

Case No.	Femoral circulation time Control	In cold	Prolongation in circulation time (sec)	Fall in rectal temperature (°F)	No. of tests
3	9.8	14.0	4.2	10.3	1
6	13.4	13.8	0.4	3.8	2
7	12.4	15.0	2.6	8.8	1
8	11.2	17.6	6.4	12.2	1
9	10.4	17.4	7.0	11.6	1
10	12.8	22.8	10.0	14.6	1
11	12.7	18.6	5.9	13.6	2
12	12.9	17.6	4.7	11.1	1
13	9.9	16.6	6.7	10.1	1
14	11.9	20.6	8.7	14.1	1
Avg	11.74	17.40	Correlation +0.81		

D. Effects of Shivering. In 2 subjects shivering was present because of insufficient depth of anesthesia during the stage of cooling. Both of these were also tested in the cold without shivering and at normal body temperature. In the first of these patients, shivering was quite pronounced. Circulation times from antecubital, jugular, and femoral veins to arterial chemoreceptors were all shorter than the corresponding times measured at normal temperatures. When the tests were repeated in the cold without shivering (*i. e.,* under deeper narcosis), the 3 circulation times were all prolonged over the control at normal temperatures.

In the second patient, shivering was only slight and was confined to the extremities. In this instance, circulation time from an antecubital vein was shorter than the control at normal temperature while the other two were increased but slightly. When retested in the cold under adequate narcosis without shivering, all 3 times were prolonged over the times recorded in controls at normal temperature.

E. Effect of Anesthesia. Three patients were used to test this factor. Examination proved them to have normal cardio-vascular systems. Circulation times were measured from the 3 sites of injection before and during evipal anesthesia. In all 3 cases the circulation times were shorter from each injection site under the anesthetic than at rest without it. Pulse rate was increased and blood pressure was lowered in all 3 cases during the narcosis.

It is probable that other types of anesthesia would produce somewhat different results. especially on blood pressure, but since evipal was used as the narcotic in most of our patients to whom any such drug was given, these observations show that the anesthetic *per se* was not a prominent factor.

F. Effects of Cooling on Pulse Rate and Blood Pressure. Pulse

rates were usually slower and blood pressure regularly lower in the cold than in the same patients at normal temperatures. In 2 instances in which pulse rate was faster in the cold, the circulation time was nevertheless prolonged.

Discussion. The overwhelming factor in the results obtained by the cyanide method must be represented by circulation through the lungs. Since pulmonary circulation time varies inversely with minute volume of the right heart and directly with capacity and resistance of the pulmonary circuit, measurement of pulmonary circulation time and its variations is a criterion of the resultant of these two factors acting simultaneously.[3, 4, 5] Our results, therefore justify the conclusion that when human patients are exposed to low enviromental temperatures by which their rectal temperatures are reduced to levels approaching 85° F, the balance between right heart minute volume and pulmonary capacity and resistance is shifted toward the latter.

A low environmental temperature reduces metabolism of brain as measured by smaller arterio-venous differences despite a slower blood flow.[6] If a similar reduction occurs in heart muscle under similar circumstances, the weaker cardiac contractions that would result could, by diminishing cardiac output, account for almost all of the prolonged circulation time as well as the slower pulse rate and lower blood pressure.

Patients in cold baths have a smaller cardiac output than controls.[7, 8] This suggests changes in right heart output as the largest factor to be considered. Although the dogs' heart will contract at temperatures as low as 77° F, the output near this lower extreme is apt to be reduced as the heart begins to fail. Our low temperatures may fall in the range of diminished cardiac output. Right heart failure with recovery has been confirmed clinically in one of these cases.[9]

Absence of correlation of extent of prolongation of antecubital-arterial chemoreceptor time with the amount of reduction of rectal temperature confirms the necessity of controlling arm temperatures

3 Stewart, G. N., *J. Physiol.*, 1894, **15**, 465.

4 Wiggers, C. J., *Physiol. Rev.*, 1921, **1**, 239.

5 Grollman, A., *The Cardiac Output of Man in Health and Disease*, C. C. Thomas, Springfield, Ill., 1932.

6 Fazekas, J. F., and Himwich, H. E., PROC. SOC. EXP. BIOL. AND MED., 1939, **42**, 537.

7 Eismayer, G., and Czyrnick, W., *Z. Kreislaufforchg.*, 1934, **26**, 226.

8 Bornstein, A., Budelmann, G., and Ronnell, S., *Z. Klin. Med.*, 1931, **118**, 596.

9 McNair-Scott, T., personal communication.

when using the antecubital vein as a point of injection and the difficulty in interpretation of results obtained.[10]

A significant correlation of femoral-arterial chemoreceptor time with rectal temperature suggests that in the tissues which contribute blood to this long extent of intraäbdominal and intrathoracic vein, the volume of blood flow is reduced in direct proportion to the decrease in internal (rectal) body temperature, while in the case of the arm and head this is not true. It has been suggested that this correlation may be an expression of Van't Hoff's Law.[11, 12]

Summary. Pulmonary circulation time is prolonged in humans whose internal temperature is reduced toward 85°F when exposed to low environmental temperatures. It is suggested that diminished output of the right heart is a large factor. Correlations between fall in rectal temperature and prolongation in circulation time exist only when the femoral vein is the site of injection. Shivering shortens circulation time or minimizes prolongation due to hypothermia.

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Reflex Inhibition of Bile Flow and Intestinal Motility Mediated Through Decentralized Celiac Plexus.

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The celiac ganglia are anatomically and functionally related to the splanchnic nerves. The peripheral links in splanchnic efferent conduction pathways are made up of celiac ganglion cells. Splanchnic nerve components, however, are not the only nerve fibers which terminate in the celiac ganglia. In a recent experimental anatomical study, terminal branches of axons have been demonstrated in preparations of the celiac ganglia of the cat in which all the splanchnic nerve fibers which enter these ganglia had undergone degeneration, following bilateral section of the splanchnic nerves. Intact nerve fibers also have been demonstrated in sections of the distal segments of divided mesenteric nerves arising from the celiac plexus, after the fibers separated from their cells of origin had undergone degeneration.[1] These findings support the assumption that axons of

[10] Stead, E. A., Jr., and Kunkel, F., *Am. J. Med. Sc.*, 1939, **198**, 49.

[11] Ring, G. C., *Am. J. Physiol.*, 1939, **125**, 244.

[12] Bruhn, J. M., *Am. J. Physiol.*, 1940, **129**, 322.

[1] Kuntz, A., *J. Comp. Neur.*, 1938, **69**, 1.