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Influence of Hypothermia and Hyperthermia on Survival Time of Dogs in Hemorrhagic Shock.*†

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During the past 3 years researches in this laboratory[1] have convinced us (1) that hemorrhage which leads to severe and protracted hypotension leads to an irreversible state from which the animal dies after reinfusion of all the blood withdrawn, (2) that the cardio- and hemo-dynamic course of events is identical with that observed in other types of shock, and (3) that shock so produced by standardized bleeding eventuates in death within 2-8 hours in 75 to 80% of dogs under morphine-barbital anesthesia or, expressed otherwise, may be said to offer an animal a 20-25% chance of maintaining their arterial pressures at reasonably normal levels for 4 to 6 hours.

This report concerns itself with the use of the method for comparing the effects of hypo- and hyperthermia on total survival time. The method for producing standardized hemorrhagic shock in dogs anesthetized with morphine and barbital has been described previously.[1] It consists, briefly, in withdrawing blood rapidly until mean arterial pressure has fallen to 50 mm Hg., in holding it at this level for 90 minutes by repeated small withdrawals of blood, in subsequently reducing mean arterial pressure to 30 mm Hg. for 45 minutes, in reinfusing the withdrawn blood (heparinized)‡ and observing the trend of arterial pressures 4-6 hours thereafter. If the pressure declined to 50 mm Hg. or the animal died, shock had occurred; if the animal maintained normal blood pressures 6 hours or better, a nonshock state was declared to exist. In the present experiments *the time of survival* after reinfusion of blood was chosen as a criterion. Operative procedures were kept at a minimum and consisted only in cannulation of the femoral arteries for bleeding and registration of mean arterial pressures and of a femoral vein for reinfusion.

Survival times of hyperthermic animals submitted to standardized bleeding were available in the case of 17 animals previously used by other groups in this laboratory[1] during the hot summer months of 1942 when room temperatures ranged from 26 to 33°C and rectal temperatures of the dogs varied from 38.8 to 40.1 C. To these were added 7 more animals studied under similar conditions during hot summer days in 1943. Their rectal temperatures ranged from 38.3 to 41.7°C.

For comparison, a series of 20 dogs was submitted to the standardized bleeding while their bodies were cooled in a semi-insulated box at environmental air temperatures of 15-20°C, and with radiating wall surfaces slightly above that of melting ice. In a few instances, ice bags were also applied for short intervals of time when it seemed desirable to hasten the reduction of body temperature.

In all of these experiments the temperature of the box air, of the trunk, extremities, ears, and rectum were continuously recorded at 6-minute intervals by a "Micromax" recorder. It was found difficult, however, to maintain animals in such cooled environments at a strictly constant temperature owing to changes in arterial pressure, blood flow in the skin and

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1 Werle, J. M., Cosby, R. S., and Wiggers, C. J., *Am. J. Physiol.*, 1942, **136**, 401; Wiggers, C. J., and Werle, J. M., PROC. SOC. EXP. BIOL. AND MED., 1942, **49**, 604; Huizenga, K. A., Brofman, B. L., and Wiggers, C. J., *Idem*, 1943, **52**, 77; *J. Pharm. and Exp. Therap.*, 1943, **78**, 139; Wiggers, H. C., and Middleton, S., *Am. J. Physiol.*, 1944, **140**, 677.

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TABLE I.

Hyperthermic Animals. Dog No.	Effective mean temp., °C	Survival period, hr	Hypothermic Animals Dog No.	Effective mean temp., °C	Survival period, hr
17A	38.8	3.1	9C	28.3	2.5
10A	38.8	3.3	18C	29.4	24.8
15A	38.8	3.7	2C	30.6	13.3
3A	38.8	4.3	14C	30.4	*
5A	38.9	4.2	16C	30.6	13.0
12A	38.9	3.0	19.C	30.8	20.0
6A	39.0	7.8	3C	31.8	14.5
11A	39.2	5.5	5C	31.5	11.5
AA	39.2	12.0	7C	31.5	4.3
13A	39.2	13.0	17C	32.4	12.0
2A	40.0	2.5	4C	32.9	14.5
4A	40.0	2.8	1C	33.0	9.2
7A	40.0	4.9	20C	33.4	20.0
8A	40.0	5.4	15C	33.1	9.0
			13C	35.6	33.5
	40.1	2.8	11C	35.4	20.0
14A	40.1	4.5	5C	35.5	4.5
16A	40.1	4.8	12C	35.6	33.5
			8C	36.1	3.0
4B	38.3	12.0	10C	36.7	31.5
6B	38.5	4.8			
5B	38.9	3.5		Avg	15.4
2B	39.7	2.0		Range	3-33.5
7B	40.0	3.2		(excluding 14C)	
1B	40.3	11.5		Mode	13.9
3B	41.7	3.2		S	10.45
			*Sacrificed 6 days		
Avg		5.3			
Range		2-13 hrs			
Mode		4.25			
S		3.34			

metabolic rate produced by withdrawal and reinfusion of blood. Consequently, an "effective average rectal temperature" was calculated for each hypothermic animal by taking the average of the temperatures which obtained during the periods of 50 mm Hg. hypotension, of 30 mm Hg. hypotension, and either of the 4 hours after reinfusion or of a lesser time when the animal died sooner.

Results. The results of all experiments on hyperthermic and hypothermic animals, all submitted to identical standardized bleeding, are summarized in Table I. These are rearranged in accordance with the effective average rectal temperatures of the animals during the experimental periods. A glance indicates that the average and most of the individual survival periods are definitely longer in animals whose rectal temperature was kept below 37°C than in those in whom it ranged above this level. The differences are statistically significant. On the other hand, it must also be noted that with one exception (Dog 14-C), all animals succumbed. Autopsies were performed on all but one of the cooled dogs, *viz.*, the one that lived for 6 days after the experiment. In all but 3 animals the duodenum showed mucosal changes varying from a slight streaky hyperemia (1+) to intense congestion, edema, and bloody fluid in the lumen (3+). In 13 animals this extended far down into the jejunum and ileum (4+). In 15 animals, intense congestion of the rectum and sigmoid was also present. In all except 6 of the animals subendocardial hemorrhages were found varying from a few small petechiæ, 1-3 mm in diameter, to large confluent hemorrhages, 1-3 cm in diameter. Hence, while cooling of the body tends to prolong life after damage due to prolonged severe hemorrhagic hypotension it does not lead to recovery under these conditions.

The practical value of such an extension of the survival time is debatable. It has often

been stated that it is the first duty of a physician to keep a patient alive so that he may be given a chance of being cured later. However, until such chances are increased beyond what they appear to be at present, in the case of our standardized hemorrhagic shock, the practical value of maintaining a somewhat lower body temperature appears vanishingly small. However, it must be kept in mind that the shock induced in our animals is of a severe form and the possibility exists that hypothermia may be of greater benefit in other types of shock.

Summary. Observations on 44 dogs submitted to standardized bleeding and reinfusion procedures which induce irreversible hemorrhagic shock showed that the survival period following reinfusion of heparinized blood is definitely extended by a hypothermic state, but with one exception all dogs succumbed.

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Metabolic Studies in Patients with Cancer of the Gastro-Intestinal Tract. XX. Lipotropic Properties of Protein.*

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Recent studies from these laboratories have demonstrated the value of protein-rich diets in the treatment of the hepatic dysfunction of patients with gastro-intestinal cancer. This conclusion has been based chiefly upon the increased functional capacity of the liver as determined by multiple function tests. The livers of these patients, when untreated, almost uniformly contain at laparotomy abnormally high concentrations of lipid and probably low concentrations of glycogen,[1] and there is reason to believe that this unusual chemical constitution, in turn, may account for a part of the reduced functional state of the organ.[2,3] In an earlier investigation it was demonstrated that the livers of patients with gastro-intestinal cancer readily could be depleted of their excess fat. One method by which this could be accomplished was by the oral administration of inositol or lipocaic merely during the night preceding operation.[4] For these reasons, it appeared desirable to learn if the return towards normal hepatic function induced by the feeding of high protein diets to the patients studied was associated with the restoration of a normal chemical composition of their livers.

Methods. The methods used in the present study have been described in previous communications.[1,4]

Results. In a previous investigation[1] the concentrations of lipid in the livers of 28 patients with gastro-intestinal cancer who came to laparotomy after the usual 10-hour preoperative fast ranged from 5.3 to 35.0 g and averaged 16.40 g %. The glycogen content of these livers, in turn, varied from 0.5 to 8.3 g and averaged 2.56 g %.

In contrast, the concentrations of fat in the livers of 7 patients with gastro-intestinal cancer who ingested 2.5 g of complete protein per kg per day for from 10 to 21 days, were all

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2 Conner, C. L., *Am. J. Path.*, 1938, **14**, 347.

3 Soskin, S., and Hyman, M., *Arch. Int. Med.*, 1939, **64**, 1265.

4 Abels, J. C., Ariel, I. M., Murphy, H. T., Pack, G. T., and Rhoads, C. P., *Ann. Int. Med.*