THE CARDIOVASCULAR effects of hypothermia in animals have been studied extensively. However, little information is available concerning the effects of hypothermia on renal function. The present report is concerned with changes in filtration rate, renal blood flow and $\text{Tm}_{\text{PAH}}$ in the hypothermic dog. The effects of hypothermia on the renal excretion of water and electrolytes will be the subject of a separate report.

METHODS

Experiments were done in two constant temperature rooms. One room, maintained at +20°C, was used to obtain control observations. The other room, maintained at -25°C to -30°C, was used for inducing hypothermia. Continuous temperature records for both rooms were obtained by means of Brown recording thermographs.

Healthy mongrel female dogs, ranging in weight from 7.6-22.4 kg, were used in the study. The animals were kept in the constant temperature room at +20°C for at least 5 days preceding experiments. Food was removed 24 hours before experiments. Large or long-haired dogs were clipped, leaving the fur 1 in. long.

At the beginning of the experiments, the animals were anesthetized with intraperitoneal injections of pentobarbital sodium (30 mg/kg) and control observations were made in the constant temperature room at +20°C. After appropriate priming injections, infusions of $\text{p}$-aminomannitol solution were administered at 3.5 cc/min. by means of a Bowman constant infusion pump. After three control clearance periods of 15-20 minutes each, the animals were quickly transferred to the cold room, maintained at -25°C to -30°C, and collection of urine and blood was resumed. The transfer, which necessitated interrupting the constant infusion, was completed within 1 or 2 minutes. To prevent freezing in the cold room, solutions were infused through a plastic catheter which was interwound with a warming coil and insulated with an outer layer of plastic tubing. Urine was collected continuously into graduated cylinders, through a rubber bladder catheter on which a 500-watt heating lamp was directed. Blood was obtained at appropriate intervals from the femoral artery by means of an inlying plastic cannula, and was drawn into syringes moistened with heparin. A copper-constantin thermocouple was inserted 15-20 cm into the rectum, and rectal temperature was recorded at 5-minute intervals with a Brown potentiometer.

During induction of hypothermia, urine collections were 15-20 minutes in duration, each period embracing a decline in rectal temperature of roughly 1°C. The rate of infusion of PAH and creatinine was progressively decreased as the rectal temperature (and renal functions) declined, in order to keep the plasma concentrations of these substances constant. Experiments were discarded when the concentrations of infused substances failed to remain constant within narrow limits.

In most experiments, observations were continued until urine formation ceased, and no attempt was made to revive the animal. However, in four dogs, experiments were terminated at rectal temperatures above 25°C. These animals were removed from the cold room, allowed to rewarm spontaneously, and were subsequently used for additional experiments.

To determine the extraction ratio of PAH (E$_{\text{PAH}}$) during hypothermia, two dogs were prepared with the right kidney explanted to the subcutaneous tissue of the flank as described by Rhoads (1). In experiments on these animals, blood was drawn simultaneously from the right renal vein and the left femoral artery. Samples were not chilled, but were centrifuged within 5 minutes after they were drawn.

The glomerular filtration rate (GFR) was measured as the exogenous creatinine clearance, creatinine being determined by the method of Bonsnes and Taussky (2). Effective renal plasma flow (ERPF) was measured as the PAH clearance, using the method of Smith et al. (3) to determine PAH. $\text{Tm}_{\text{PAH}}$ was determined at L/T ratios of 1.5-4.5 (4), assuming a protein binding factor of 0.92 for dog plasma (5). The oxygen content of whole blood was determined as described by Peters and Van Slyke (6). Samples of blood for oxygen determination were drawn into oily, heparinized syringes. They were kept at 10°C until oxygen analyses were done within 4 hours after collection. The hematocrit of arterial blood samples was determined by the Wintrobe (7) method.

The author is grateful to Dr. Fletcher Miller for performing the surgery on these animals.
RESULTS

Twenty-one experiments in 15 dogs were technically satisfactory. Twelve other experiments were discarded for various reasons, the most common being inconstancy in the plasma concentrations of PAH and creatinine.

Vigorous shivering usually occurred soon after the animal was placed in the cold room, but diminished as the rectal temperature declined and was usually absent below 27°C. Rectal temperature usually remained near the control value for the first 10 or 15 minutes in the cold room. Thereafter, the rate of decline in rectal temperature was approximately linear, and in analyzing the data, the rectal temperature at the mid-point of each urine collection period is taken as the average for the period.

The urine flow varied with the rate of infusion of 5% mannitol and usually remained well over 1.0 cc/min. In most instances the experiment was continued until an abrupt decrease in urine flow to nearly zero occurred at a rectal temperature between 20° and 25°C. This sudden decrease in urine flow coincided with the onset of marked respiratory depression, as evidenced by cyanosis of mucous membranes and arterial blood samples. However, respiration was apparently unimpaired until near the end of the experiment. Arterial oxygen content, determined in five dogs, was in the normal range until a few minutes before the abrupt decrease in urine flow which marked the end of the experiment.

Studies of mean arterial pressure during hypothermia in the dog (8–10) indicate that pressure generally stays above 90 mm of Hg until the rectal temperature falls below 25°C. Observations were made in two dogs which confirm this finding with the cooling technique used in our experiments.

Glomerular Filtration Rate and Effective Renal Plasma Flow. During progressive hypothermia, GFR and ERPF are approximately linear functions of rectal temperature. The data presented here were obtained during pentobarbital anesthesia. However, the same relationships are apparent with chloralose anesthesia (7 expers.), Tubocurarine Chloride (3 expers.) and chlorpromazine (1 exper.).

Figure 1 shows the simultaneously determined GFR and ERPF in relation to temperature for six experiments. Renal plasma flow is increased as cooling begins, reaching an average maximum at 117% of the control value (range 104–131%). This trend is not usually apparent in the data on filtration rate, which show an average maximum during cooling at 99.3% of the control value (range 91–115%). The magnitude of the initial increase in ERPF appears to be roughly correlated with shivering. It does not occur in experiments where shivering is inhibited with curare or in dogs (not included in the data) deeply anesthetized with pentobarbital. Maximal values for ERPF are reached at rectal temperatures above 34°C. During progressive hypothermia, renal plasma flow decreases more rapidly than filtration rate as rectal temperature declines (fig. 1).

The linear regressions of filtration rate on rectal temperature were calculated for 13 dogs. The weighted mean regression for this group shows an average rate of decrease in GFR of 5.36% of the control value per degree decrease in rectal temperature (range 4.26–7.28%). Linear regressions of renal plasma flow on rectal temperature were calculated for five dogs. The average rate of decrease in ERPF is 8.24% of the control value per degree decrease in rectal temperature (range 6.52–9.77%).

Data on filtration fraction are presented in figure 2. The curvilinear regressions were derived from linear regressions of simultaneously measured GFR and ERPF on rectal temperature. Filtration fraction exhibits a progressive increase as rectal temperature declines, although the magnitude of the increase is variable. The average regression increases from 0.28 at 38°C to 0.39 at 26°C.

Renal Blood Flow. In our experiments, the hematocrit of arterial blood is increased by 8–22%, a finding previously reported (8, 11, 12) in hypothermic animals and man. Sometimes the increase is gradual but more often an abrupt rise in hematocrit occurs soon after the animal is placed in the cold room, probably due to mobilization of cells from the spleen and other stores. The renal blood flow, as calculated from renal plasma flow and hematocrit, is increased proportionally more than renal plasma flow during shivering, reaching

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FIG. 1. Linear regressions of GFR (open circles) and ERPF (solid dots) expressed as percentages of control values on rectal temperature in degrees centigrade. Each point represents one clearance period.

120-145% of the control value at rectal temperatures above 34°C. Since the hematocrit continues to increase as hypothermia progresses, renal blood flow remains proportionally higher than renal plasma flow as the rectal temperature decreases. Renal blood flow is often greater than the control value until rectal temperature reaches 32-33°C and ERPF is reduced by 15-20%.

**Extraction Ratio of PAH.** Technical diffi-
cultics were frequently encountered in attempts to determine $E_{PAH}$ during hypothermia. However, three satisfactory experiments were done on one dog. An autopsy on this animal revealed an essentially normal explanted kidney with some capsular thickening and low grade pyelitis. The opposite kidney showed no pathological change. Table 1 details results in two experiments. Sixteen extraction ratios were obtained at rectal temperatures ranging from 38.2-27.5°C. Values for $E_{PAH}$ range from 69.7-84.0% and average 76.7%. The values are lower than those reported by Phillips et al. (13) in normal dogs, a circumstance probably due to diffusion of PAH from cells to plasma during centrifugation (4, 13) since the samples were not chilled. However, $E_{PAH}$ showed no tendency to decrease with rectal temperature and its seems reasonable to conclude that $E_{PAH}$ is unimpaired during hypothermia.

$Tm_{PAH}$. Observations on $Tm_{PAH}$ were made during progressive hypothermia in five dogs. Data from these experiments are presented in figure 3. In dog 21 the control value for $Tm_{PAH}$ is abnormally low relative to body weight (0.32 mg/kg) and data on this animal have been analyzed separately. During the initial cooling period, an increase in $Tm_{PAH}$ occurs and reaches a maximal value above 34°C. This averages 113% of the control value for the four normal dogs, and is 119% in dog 21. The temperature coefficient ($Q_{lo}$) on the four normal dogs ranges from 3.42-3.84 and averages 3.62. In dog 21, $Q_{lo}$ is 2.52.

An Arrhenius temperature plot for the four normal dogs is given in figure 4, where the natural logarithm of $Tm_{PAH}$ is related to the reciprocal of the absolute temperature. The data are linearly disposed when expressed in this form, with the exception of the last clearance period in each experiment, possibly indicating that hypoxia or other factors in addition to temperature are influencing $Tm_{PAH}$ at the end of the experiment. These terminal periods are therefore excluded in the calculation of the linear regressions. The temperature characteristic, $\mu$, calculated with the Arrhenius equation, averages 23,540 Cal/M for the four normal dogs. Values for individual animals are given in the figure, and all are within 10% of the mean. However, for dog 21, $\mu = 16,400$ cal/M.

Effect of Repeated Experiments on the Same Animal. Experiments involving hypothermia were done twice in each of two animals, and three times in each of two other animals. Repeated observations on the same animal were made at intervals of several weeks. Except for the last experiment on each animal, these experiments were terminated at rectal temperatures between 25° and 29°C, and the animals were allowed to rewarm spontaneously. Data from repeated experiments on the same animal show rather consistent renal circulatory responses to hypothermia. Data from two experiments on dog 13 are shown in figure 1 and table 1. Comparison of control values for GFR and ERPF in repeated experiments gives no indication of residual impairment in renal function resulting from hypothermia.

**DISCUSSION**

In hypothermic human subjects, Talbott (14) found a linear relationship between filtration rate and rectal temperature. Renal plasma flow decreased proportionally more than filtration rate in his subjects and filtration fraction increased. Our data show a similar renal circulatory response to hypothermia in the dog.

The changes in renal plasma flow which we observed appear to run parallel to the changes in cardiac output observed by others (9, 15, 115, 20).

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4 Performed by Capt. Roy Korson, Army Medical Research Laboratory.
TABLE I. RENAL BLOOD FLOW AND E\(\text{PAH}\) DURING HYPOTHERMIA

<table>
<thead>
<tr>
<th>Rectal Temp</th>
<th>GFR (cc/min)</th>
<th>ERPF (cc/min)</th>
<th>Hct (%)</th>
<th>ERBF (cc/min)</th>
<th>E(\text{PAH})</th>
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Exper. D, dog 1, wt. = 19.2 kg

Exper. L, dog 1, wt. = 19.2 kg

Progressive hypothermia

16) during hypothermia. Rosenhain and Penrod (15) report that between rectal temperatures of 35°C and 25°C, cardiac output shows a linear decrease. This is approximately the same temperature range in which we have found a linear decrease in renal plasma flow. Also, during the early phase of cooling, when shivering is at a maximum, cardiac output (9) and renal plasma flow are both increased by as much as 25 or 30%. When shivering is inhibited, an initial increase in cardiac output does not occur (16). The initial increase in renal plasma flow is likewise abolished in our experiments when shivering is inhibited by curare or deep anesthesia. These facts suggest that the changes in renal plasma flow which we observed are primarily dependent on changes in cardiac output.

A variable increase in filtration fraction occurs in our experiments, probably indicating that the renal circulation participates in a general increase in peripheral resistance (16) during hypothermia. However, the renal blood flow, as calculated from renal plasma flow and hematocrit, remains high until rectal temperature is substantially reduced. The high values for renal blood flow suggest that the kidneys receive a large fraction of the cardiac output. The renal circulation may be favored at the expense of other tissues during hypothermia as it is in experimentally reduced cardiac output (17).

In deep hypothermia, increased blood viscosity (11, 18) may be partly responsible for the observed decrease in renal blood flow, although in dogs subjected to simulated high altitude (19), increased blood viscosity does not retard renal plasma flow.

There are few data available on the effects of temperature on Tm\(\text{PAH}\). Forster (20) reports a Q10 of 2.0 in marine fish over the temperature range of 17-7°C. Goldring et al. (21) observed that Tm\(\text{Diodrast}\) is sensitive to changes in temperature, and suggest a Q10 of 2.0 as the Figure 3. Tm\(\text{PAH}\) expressed as a percentage of control value in relation to rectal temperature in degrees centigrade. Each point represents one clearance period.
basis for correcting results to normal body temperature. This figure is also recommended (4) for correcting $T_{\text{PAH}}$. We have found an average $Q_{10}$ of 3.62 in four normal dogs. However, our determinations were made in the hypothermic temperature range and would not apply to normal or elevated temperatures, since $Q_{10}$ will decrease as temperature rises.

Inasmuch as renal blood flow and $T_{\text{PAH}}$ vary in the same direction during progressive hypothermia, the possibility cannot be excluded that the changes in $T_{\text{PAH}}$ observed in these experiments may be partly dependent on simultaneous changes in blood flow. On the other hand, tubular transport maxima are directly sensitive to small changes in body temperature (21). Furthermore, studies of tubular transport maxima (22, 23) are, with one exception (24) in agreement that these functions are unaffected by moderate variations in renal blood flow. It seems probable, therefore, that the changes in $T_{\text{PAH}}$ observed during hypothermia are, for the most part, directly dependent on temperature rather than on concurrent changes in blood flow. This interpretation is supported by the close grouping of the data in the Arrhenius temperature plot (fig. 4).

According to Crozier (25) the temperature characteristic, $\mu$, should define the activation energy of the rate limiting reaction for $T_{\text{PAH}}$, although it would not be possible to identify this reaction from our data. Values for $\mu$ observed in four normal dogs average 23,500 cal/\(\text{m}^2\). It is of interest that a different value (16,400 cal/\(\text{m}^2\)) was observed in one dog in

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**Figure 4.** Arrhenius temperature plot. The natural logarithm of $T_{\text{PAH}}$ in relation to the reciprocal of the rectal temperature in degrees absolute for four dogs. Each point represents one clearance period.
which \( T_{\text{PAH}} \) is abnormally low. In Crozier's view, this would imply that PAH transport is limited by a different reaction in this abnormal animal.

In man, hypothermia is often associated with albuminuria, and abnormalities in formed elements (26, 27) in the urine, although in subjects who have died following hypothermia, no pathological changes have been found in the kidney (28, 29). Talbott (28, 30) states that when fluid intake is adequate, routine urinalyses show no abnormalities. Our experiments were not designed to detect abnormalities in the urine. However, results of repeated experiments in four dogs gave no evidence of residual impairment in GFR or ERPF following one or two episodes of hypothermia, and an autopsy on one dog after three experiments showed no pathologic changes attributable to hypothermia.

**SUMMARY AND CONCLUSIONS**

Renal function studies were made in 21 experiments on anesthetized dogs during progressive hypothermia induced by exposure in air at \(-25^\circ\text{C} \text{ to } -30^\circ\text{C}\). Results are compared to control observations made immediately prior to induction of hypothermia. When dogs are placed in the cold, renal plasma flow at first increases by an amount roughly correlated with shivering, and reaches a maximum which for five dogs averages 117% of the control value. The maximum is reached at a rectal temperature between 38° and 34°C. During progressive hypothermia, filtration rate and renal plasma flow decrease as approximately linear functions of rectal temperature. The rate of decrease in filtration rate for 13 dogs averages 1.36% of the control value per degree decrease in rectal temperature. The rate of decrease in renal plasma flow is more rapid, averaging 8.24% of the control value per degree decrease in rectal temperature. Filtration fraction is progressively increased during hypothermia, but the magnitude of the increase is variable. Because of a progressive increase in hematocrit during hypothermia, renal blood flow is initially increased by a greater relative amount than is renal plasma flow. Renal blood flow reaches a maximum during shivering at 120 145% of the control and remains above the control value until rectal temperature reaches 32–33°C. The extraction ratio of PAH is unaffected by changes in rectal temperature ranging from 38.2–77.5°C. \( T_{\text{PAH}} \) is increased during shivering and subsequently decreases as rectal temperature declines. The temperature coefficient \( (Q_{10}) \) in the hypothermic range averages 3.62 for four dogs. The temperature characteristic, \( \mu \), calculated from the Arrhenius equation, averages 23,500 cal/m. Dogs subjected to repeated experiments exhibit no evidence of residual change in renal function resulting from hypothermia.

Statistical analysis was done by Capt. George Saiger, biometrician, Army Medical Research Laboratory. The author is also indebted to Dr. A. D. Keller for the use of laboratory facilities and to Mr. T. W. De Murnbrun for assistance with the work.

**REFERENCES**

29. Smith, L. W. Arch. Path. 30: 424, 1940.