J. Physiol. (1956) 133, 334–346

THE DISTRIBUTION AND REGULATION OF TEMPERATURE IN THE RAT

By J. GRAYSON and D. MENDEL

From the Department of Physiology, University College, Ibadan

(*Received* 27 *February* 1956)

That mammals can thrive under widely different conditions of environmental temperature is an accepted fact, but the mechanism by which this is made possible is still far from clear. A knowledge of temperature distribution in internal organs is vital to its study, but although much is known about animals bred in temperate climates (Federov & Shur, 1942), and work has been carried out on cold acclimitization (Fregly, 1953), little has been published concerning temperature distribution in animals bred in a tropical environment. Even less is known about the adaptations which occur in internal temperature when an animal is exposed to a sudden change in environmental temperature. The study of these two matters has been the object of the present work.

METHODS

Copper-constantan thermocouples made from 36 s.w.g. copper and constantan wire were used for temperature recording. A junction box (Lewis, 1930) was used so that readings could be taken from several points. Recording was by means of a Cambridge 'spot' galvanometer calibrated to read directly to 0·2° C.

Wistar strain male rats, born and bred in the tropics, and of average weight 220 g were used. Temperatures were recorded from the liver, spleen, upper abdomen between the liver and diaphragm, the mesentery as near as possible to the portal vein, and the lower abdomen, the thermocouple occupying a variable position in the pelvic cavity. Thermocouples were introduced under ether anaesthesia, through a midline abdominal incision and sutured in place in the appropriate organ through a loop in the wire (Birnie & Grayson, 1952). The presence of the thermocouples seemed to have no ill effect on the weight, appetite or general well-being of the rats. Most observations were made with the animals restrained in tubes made from perforated zinc, an oval hole in the top of the tube giving access to the thermocouple leads, which were freshly soldered at each experiment to the leads from the junction box. The cold environment was provided by an ordinary domestic refrigerator, its temperature being normally adjusted to remain at 7° C.

In a few experiments liver blood flow also was determined by the method of internal calorimetry which makes use of a heated thermocouple implanted in the liver. This method has been described in full (Grayson, 1952). The fundamental measurement is of liver thermal conductivity and present results are expressed in terms of conductivity increment, i.e. excess thermal conductivity in living liver as compared with the thermal conductivity of dead liver.

RESULTS

The distribution of temperature in the normal rat

In each of thirty-five experiments a thermocouple was implanted in the liver. Additional thermocouples were placed in the mesentery (21 experiments), lower abdomen (15 experiments), upper abdomen (14 experiments) and the spleen (6 experiments). Usually not more than three thermocouples were implanted in any one animal.

TABLE 1. The mean temperatures of liver, mesentery and lower abdomen in conscious resting rats

	No. of animals	Mean temp. (° C)	S.E. of mean
Liver	35	39·3	±0·24
Mesentery	21	39·1	±0·24
Lower abdomen	15	38·5	±0·20

TABLE 2. The distribution of temperature (° C) between liver, mesentery, upper and lower abdomen and spleen in conscious, resting rats

Rat no.	Liver	Mesentery	Upper abdomen	Lower abdomen	Spleen
1	38·2	38·2	—	37·3	—
2	38·4	37·9	—	37·5	—
3	39·2	39·2	—	—	39·0
4	40·9	—	39·1	39·3	40·5
5	39·4	39·3	—	—	39·1
6	40·1	40·1	—	—	39·9
7	40·8	40·0	—	—	40·4
8	40·1	40·0	—	—	39·9
9	39·5	—	39·4	38·5	—
10	39·6	—	39·4	39·1	—
11	40·0	—	39·8	37·9	—
12	40·9	—	40·8	38·8	—
13	40·6	40·6	40·4	—	—
14	39·9	39·9	39·8	—	—

The results given in Tables 1 and 2 were made in restrained conscious animals, 24 hr after operation, in a laboratory at 28° C. From Table 1 it will be seen that the mean liver temperature was 39·3° C, the mean mesenteric temperature was 39·1° C and the mean temperature recorded from the lower abdomen was 38·5° C. There was, thus, no significant difference in temperature between the liver and the mesentery near the portal vein, from which it may be concluded that the blood entering the liver from the intestine via the portal vein was probably not cooler than the liver itself. In contrast, the mean temperature of the lower abdominal cavity was 0·8° C lower than liver temperature.

The figures given in Table 2 were taken from individual experiments. The liver and mesentery produced the highest temperatures in the abdominal cavity. The temperatures recorded from between the liver and the diaphragm and from the spleen were slightly lower than liver temperature.

The effect of exposure to cold on temperature distribution in the non-anaesthetized rat

The purpose of the following observations was to record the effect on the above temperature distributions of a sudden lowering of the ambient temperature from 28 to 7° C. Temperatures were recorded for a period of 15 min in the laboratory. The rat was then placed in the refrigerated chamber, and observations continued for 90 min, after which the animal was allowed to warm up in the laboratory at 28° C.

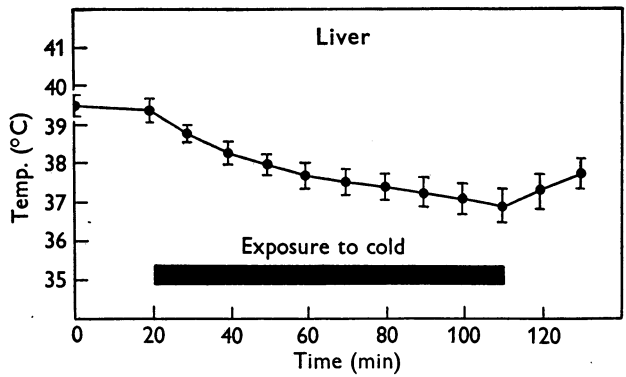

Fig. 1. Temperature responses to exposure to cold—mean of twenty-three experiments. Laboratory temperature 28·0° C. Temperature of refrigerated chamber 7·0° C. ⊕ standard error of the mean.

Fig. 1 shows the mean effect of 90 min cooling on liver temperature in twenty-three experiments on different animals. The mean drop in liver temperature over this period was 2·5° C. From Fig. 2 it can be seen that although the maximum rate of fall occurred within the first 30 min this was usually followed by a further period of 30 min during which liver temperature did not fall so rapidly, then, during the final 30 min of cooling there was, in most cases, a further slower decline in liver temperature. On removing the animal from the refrigerated chamber, recovery began immediately in most instances and near normal temperatures were regained in 30–40 min.

Fig. 2 compares the fall of liver temperature with that of the mesentery, upper abdomen, spleen and lower abdomen. The drops in mesenteric and upper abdominal temperature were similar to those occurring in the liver. The rate of cooling of the spleen was greater than that of the liver. The greatest rate of cooling was in the lower abdominal cavity.

The effect of ganglion blocking agents. In order to determine the influence of nervous factors on the rat's ability to withstand sudden drops in temperature a series of experiments was performed in which a ganglion blocking agent,

tetraethylammonium bromide (TEAB) was administered. One difficulty was to determine the effective blocking dose of TEAB. The experiments shown in Fig. 3 were performed on a single rat (220 g). Rising doses of TEAB were administered intraperitoneally on alternate days. It will be seen that with 7 mg of TEAB the maximum temperature drop in a 90 min period was 1·5° C. The effect of 14 and 20 mg of TEAB was somewhat greater and of a similar order in each case. There was an initial rapid drop of temperature complete

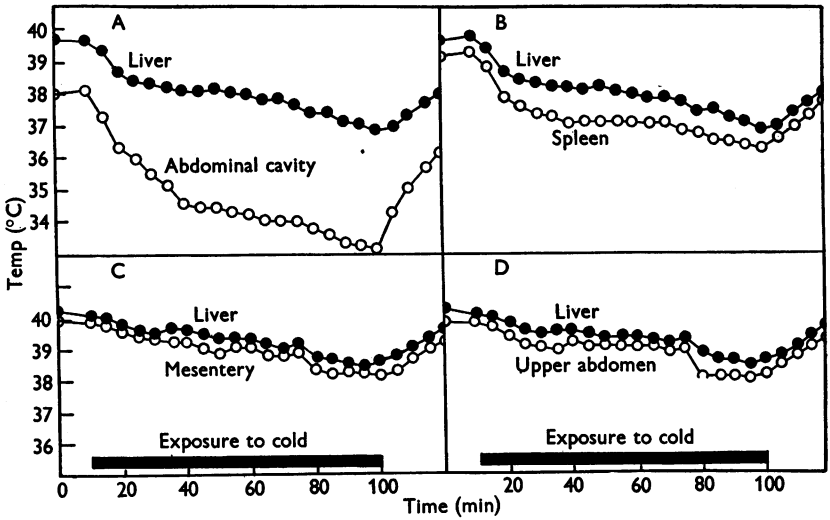

Fig. 2. Temperature responses to exposure to cold. (A) Liver and lower abdominal cavity; (B) liver and spleen; (C) liver and mesentery near portal vein; (D) liver and upper abdomen between liver and diaphragm.

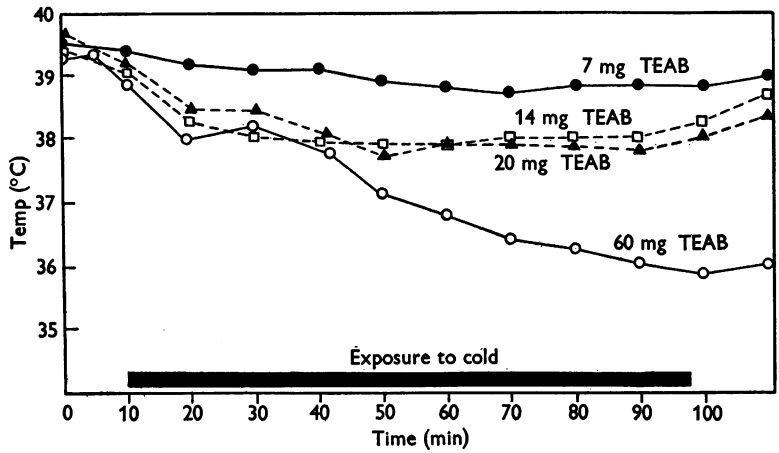

Fig. 3. Liver temperature responses to exposure to cold. The effect of different doses of TEAB. Observations made on the same rat on different days.

within 40 min. Thereafter, liver temperature remained steady. On removing the animal from the cold environment recovery began immediately but was not complete even after 40 min. Bigger doses of TEAB, 60 and 70 mg, had different effects. During the first 40 min of cooling the temperature decline was not significantly different from that produced by cold exposure after 14 and 20 mg TEAB. Thereafter, however, equilibrium was not maintained and liver temperature continued to decline.

For reasons which will be discussed later, 14–20 mg TEAB, was considered to be a full blocking dose. A number of experiments were consequently performed in which TEAB was administered in doses of 14 mg. For comparison with other procedures Fig. 4B shows a typical result. Liver temperature declined rapidly on placing the animal in the cold environment, but stabilized

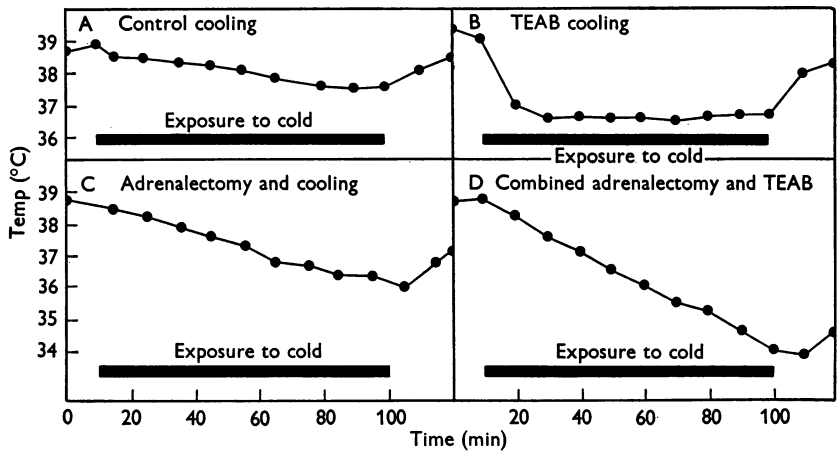

Fig. 4. Liver temperature responses in one animal to exposure to cold: (A) Control cooling; (B) after ganglion blockade; (C) after adrenalectomy; (D) after combined adrenalectomy and ganglion blockade (TEAB 7 mg).

in about 20 min. Continued exposure to cold had no further effect on the liver temperature. The effect of TEAB and cooling on mesenteric temperature and on the temperature of the upper abdomen between liver and diaphragm was similar to the effect on the liver, although throughout the 90 min period, the liver remained slightly warmer. The lower abdominal temperature and the spleen temperature both declined by amounts significantly greater than the decline in liver temperature.

The effect of adrenalectomy. In order to determine the influence of the adrenal glands on the rat's ability to withstand a sudden drop in temperature, a series of experiments was performed in which the responses to a 90 min period of cooling were investigated before and after bilateral adrenalectomy. A typical result is given in Fig. 4C. On the same animal a control cooling curve and a

cooling curve following TEAB had already been obtained (Fig. 4A, B) before adrenalectomy. The experiment shown in Fig. 4C was carried out 24 hr after the operation. There was a steady decline in liver temperature throughout the cooling period and no evidence of stabilization even after 90 min cooling. Cooling continued for 10 min after removal from the cold environment and subsequent recovery was slow. Similar results were obtained in all such experiments.

The effect of combined adrenalectomy and ganglion blockade. A small series of experiments was carried out to investigate the rat's ability to withstand exposure to cold when deprived of both nervous and adrenal mechanisms. The experiment shown in Fig. 4D was carried out 48 hr after adrenalectomy. Although only 7 mg of TEAB was given the effect was marked. There was a continuous, steady decline in temperature; the total fall after 90 min was nearly double the fall produced either by TEAB alone or by adrenalectomy alone. On removing the animal from the cold environment the temperature continued to fall for 10 min and subsequent recovery was slow.

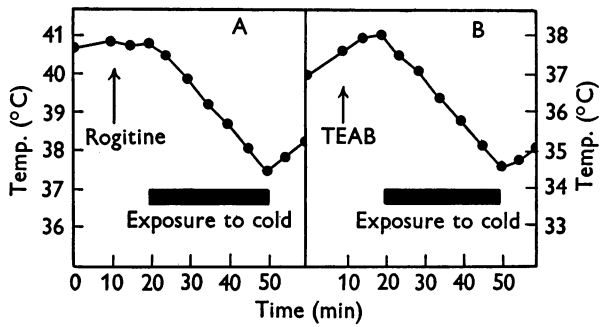

Fig. 5. Liver temperature responses in the same animal to exposure to cold: (A) after adrenergic blockade (Rogitine 1 mg i.p.); (B) after adrenalectomy and ganglion blockade (TEAB 14 mg).

The experiment shown in Fig. 5B was carried out 18 hr after adrenalectomy. 14 mg TEAB was given intraperitoneally. The rate of temperature fall was now very much greater than in previous experiments. Liver temperature declined nearly 4° C in 30 min. Similar results were obtained in all such experiments, with doses of TEAB not less than 14 mg.

The effect of Rogitine. Rogitine, 2(*N*-*p*-tolyl-*N*-*m*-hydroxyphenylamino-methyl)-imidazoline methanesulphonate (Ciba), is an effective adrenergic blocking agent reputed to inhibit specifically the response of the effector cell to the sympathetic transmitter and to circulating sympathomimetic agents. Fig. 5A shows an experiment in which 1·0 mg of Rogitine was administered intraperitoneally. The animal was subsequently placed in the cold environment. Liver temperature declined gradually, and in a 30 min period there was a total drop of about 4·0° C. In three experiments cooling was continued for

90 min and in each instance liver temperature fell to between 29 and 27° C. Fig. 5B shows in the same animal the result of cooling after adrenalectomy together with ganglion blockade. It will be apparent that the degree of cooling in Fig. 5A and B is very similar and that the curves are of much the same form. In all experiments the effect of cooling after Rogitine was qualitatively and quantitatively similar to the effect of cooling after adrenalectomy combined with ganglion blockade.

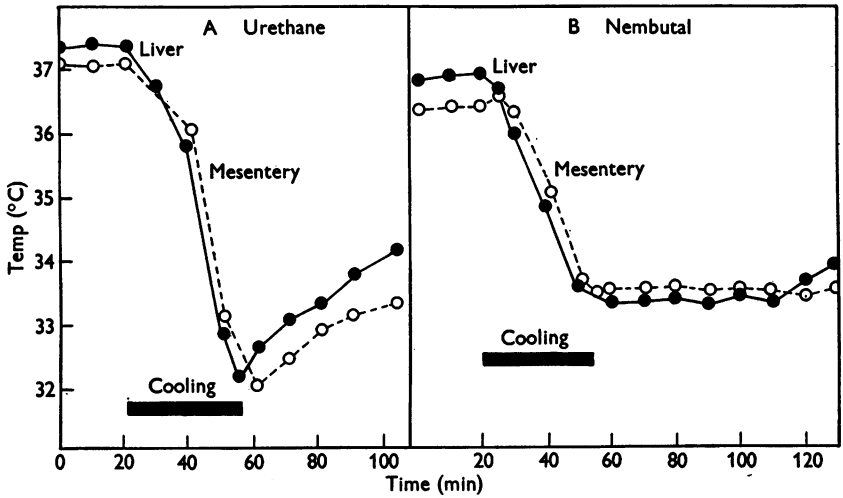

Fig. 6. Temperature responses of liver and mesentery (near the portal vein): (A) after urethane anaesthesia; (B) after Nembutal anaesthesia.

The effect of exposure to cold on temperature distribution in the anaesthetized rat

The effects of pentobarbitone sodium (Nembutal) and urethane on the ability of the rat to withstand exposure to cold were investigated. Temperatures were recorded from the liver and mesentery in all cases. Fig. 6 shows a typical result. It will be seen that with intraperitoneal urethane anaesthesia (0·5 ml., 25% (w/v) solution), in a 30 min cooling period there was a drop in liver temperature of about 5° C. With intraperitoneal pentobarbitone sodium in a dose of 0·5 mg/100 g body weight there was a drop of about 3·5° C in liver temperature.

An important finding in these experiments was that the drop in liver temperature was usually greater than the drop in mesenteric temperature. In Table 3 it will be seen that control cooling and cooling after adrenergic blockade produced similar declines in liver and mesenteric temperatures. With pentobarbitone sodium, cooling caused a mean decline in liver temperature of 3·3° C and a decline in mesenteric temperature of 2·6° C.

From Table 3 it will also be apparent that quantitatively the anaesthetic dose of pentobarbitone sodium used was less effective as a cooling agent than Rogitine, which was nevertheless safer in use. Exposure to cold of the anaesthetized animal occasionally caused death; recovery was always slow, often taking as long as 24 hr before a complete return of temperature to normal. Of a series of six rats none died as a result of exposure to cold after Rogitine.

The effect of splenectomy. To investigate the possibility of cold blood reaching the liver via the spleen, experiments were performed before and after splenectomy on animals anaesthetized with pentobarbitone sodium. In three experiments liver and mesenteric temperatures were recorded. Splenectomy had no effect on the responses of the liver or mesentery to cooling.

TABLE 3. The effect of adrenergic blockage and anaesthesia on the temperature drop produced in liver, mesentery and upper abdomen by exposure to cold. Temperature drop in ° C

	Control cooling 90 min	Rogitine cooling 30 min	Nembutal cooling 30 min
Liver	2·5	4·4	3·3
Mesentery	2·6	4·4	2·6
Upper abdomen	3·2	5·3	3·2

Suprahepatic temperature changes during cooling. To investigate possible heat loss through the diaphragm during cooling, suprahepatic temperatures were also recorded. From Table 3 it can be seen that, during control cooling, suprahepatic temperature fell by an average of 3·2° C, whilst that of the liver fell by an average of 2·5° C. After pentobarbitone sodium anaesthesia, during a 30 min period of cooling suprahepatic temperature fell by an average of 3·2° C, whilst the liver temperature fell by an average of 3·3° C. Examination of the individual records showed that the liver was always slightly hotter than the suprahepatic temperatures.

Liver blood-flow responses during cooling

In some experiments blood-flow reactions were also recorded during cooling, using the technique of 'internal calorimetry'. Blood-flow recorders were implanted in the liver. The following day the rats were restrained and the leads from the heated thermocouple connected to the recording apparatus.

Liver blood flow (conductivity increment) and cooling in the non-anaesthetized rat. Fig. 7 shows the results of a typical experiment in which conductivity increment was recorded for a period of 20 min with the animal at rest. The rat was then placed in the cold environment. The recording was continued but no significant change occurred during the period of cooling.

Liver blood-flow reactions to cooling after adrenergic blockade. In the experiment shown in Fig. 8 1 mg Rogitine was given intraperitoneally to a conscious rat. There was a small drop in conductivity increment (which may

have been due to the concomitant drop in blood pressure, which in separate experiments was shown to occur with these doses of Rogitine) and a slow decline in liver temperature followed. Liver blood flow stabilized at the new level and the rat was then placed in the cold environment. There was a rapid fall in liver temperature, but no significant change occurred in conductivity increment.

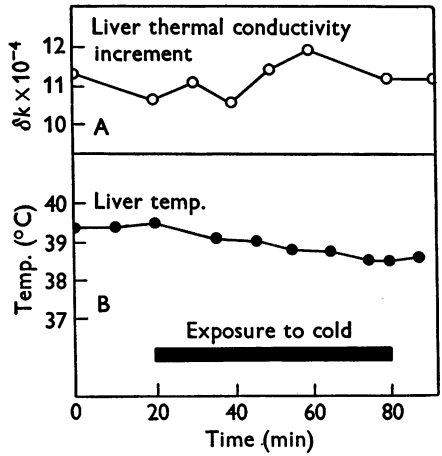

Fig. 7. Responses of the liver of an unanaesthetized rat to exposure to cold: (A) thermal conductivity increment (a function of blood flow); (B) liver temperature.

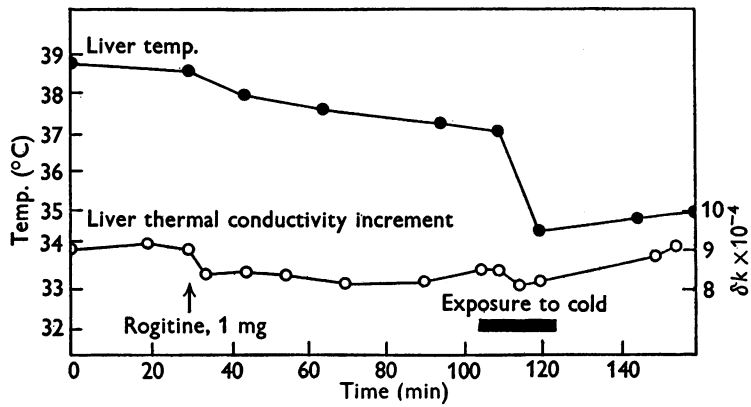

Fig. 8. Liver responses to Rogitine and cooling. Temperature and thermal conductivity increment.

Liver blood-flow reactions to cooling after pentobarbitone sodium anaesthesia. In the experiment shown in Fig. 9A a rat anaesthetized with pentobarbitone sodium was placed in the cold environment. Liver temperature declined rapidly and continuously. There was an initial, significant, drop in conductivity increment to a new level at which it stabilized; subsequently con-

ductivity increment remained stable despite the continued drop in temperature.

Liver blood-flow reactions to cooling in the splenectomized rat after pentobarbitone sodium anaesthesia. Fig. 9B shows an experiment on a splenectomized rat. Pentobarbitone sodium (1·2 mg) was given intraperitoneally, followed, after a short period of stabilization at room temperature, by exposure to cold. Liver temperature declined but there was no significant change in conductivity increment.

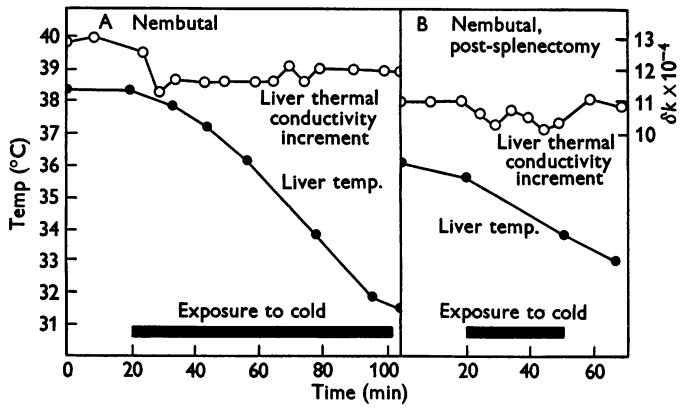

Fig. 9. Thermal conductivity and temperature responses in the liver to exposure to cold: (A) after Nembutal anaesthesia; (B) different rat splenectomized and Nembutal anaesthesia.

DISCUSSION

No previous observations appear to have been published on temperature distribution in tropical born and bred rats. The present work suggests that it is not different in rats reared in a European laboratory. Thus, in the present series, the mean liver temperature was 39·3° C. compared with a mean liver temperature of 38·7° C in an English series reported by Birnie & Grayson (1952). In both groups there was considerable difference between animals, and the differences between the means are not significant. There was similarly no difference between lower abdominal temperatures from the two series. In the rat, as in the dog (Federov & Shur, 1942), the highest intra-abdominal temperatures were found in the liver. Federov & Shur (1942) further demonstrated that portal venous temperature was slightly lower than hepatic venous temperature but considerably higher than aortic temperature. They suggested that the intestines were, therefore, important producers of heat. This suggestion is confirmed in our present work in which mesenteric temperature recorded close to the portal vein was always similar to liver temperature.

The effect of exposure to cold. In the present work rats were exposed to a sudden drop in ambient temperature of about 20° C. During a 90 min exposure,

liver temperature only fell by about 2·5° C. Most rats followed a similar pattern of reaction; there was an initial rapid fall, a period of equilibrium and a slow final fall. Without attempting to explain the detailed shape of the cooling curve it is apparent that the conscious rat has a surprising ability to withstand changes in ambient temperature. This must stem either from decreased heat elimination, from increased heat production or from a combination of the two. The sympathico-adrenal system might be expected to play an important part, particularly in relation to the control of heat elimination. Adrenalectomized rats, however, still had considerable powers of resistance; nevertheless, on exposure to cold the decline in liver temperature was gradual and continued with no sign of stabilization. In contrast, ganglion blockade by means of tetraethylammonium bromide led to a similar drop in temperature for the same duration of exposure, but the drop was relatively rapid and complete within 30 min. Thereafter stable equilibrium was maintained. These results are difficult to account for fully, but they suggest that the adrenal glands have an important part to play and, by themselves, are probably better capable of mediating stable equilibrium under conditions of cooling than is the sympathetic nervous system.

The sympathico-adrenal mechanism was totally eliminated by two methods, first, ganglion blockade combined with adrenalectomy, secondly by administration of an adrenergic blocking agent, Rogitine, in relatively massive doses. Both procedures led to the same result. Exposure to cold now produced a very rapid fall in temperature with no suggestion of equilibration after 90 min. Throughout these experiments the liver temperature remained higher than any other intra-abdominal temperature, including the mesenteric temperature. Since there was no significant change in liver blood flow it is clear that heat production in the liver continued during exposure to cold, even after elimination of the sympathico-adrenal system. The effect of ganglion blockade and adrenalectomy on resistance to cold is therefore probably mainly on the peripheral mechanisms of temperature regulation.

The action of tetraethylammonium bromide must receive further comment. The present evidence demonstrates that in a 220 g rat doses between 14 and 20 mg produce complete sympathetic blockade, since a combination of these doses with adrenalectomy produces effects indistinguishable from the effect of massive doses of a pure adrenergic blocking agent, Rogitine. Administration of bigger doses, 60 or 70 mg of tetraethylammonium bromide, however, produces a continued decline in liver temperature without equilibration. Large doses of tetraethylammonium bromide may have an adrenergic blocking action, but it is considered more likely that this is a manifestation of the curare-like action of big doses of ganglion blocking agents. If this be so then the continued cooling may be an indication of the importance of the skeletal musculature in resistance to cold.

The effect of pentobarbitone sodium. Both urethane and pentobarbitone sodium have pronounced action on resistance to cold. Birnie & Grayson (1952) showed that these agents, as well as ether, produced a drop in liver temperature greater than the drop in abdominal temperature. The present work was largely confined to a study of pentobarbitone sodium, full anaesthetic doses of which had a marked effect on the resistance to cold. Liver temperature fell rapidly, but not so rapidly as with Rogitine. It fell more rapidly than the mesenteric temperature. Such a result cannot be explained on the basis of blood-flow change, since thermal conductivity records during exposure to cold, even of the anaesthetized rat, showed no significant change.

Birnie & Grayson (1952) suggested that an excess fall in liver as compared with abdominal temperature could best be explained as due to inhibition of liver function by the anaesthetic agent. Even so the mechanism whereby the liver temperature actually falls below the temperature of the afferent blood remains to be explained. Cold blood reaching the portal vein from the spleen could scarcely be a factor since the temperature differences were not affected by splenectomy. One explanation is suggested by the observations on the temperature between the liver and the diaphragm. In the normal animal exposed to a laboratory at 28·5° C the suprahepatic temperature was only slightly lower than in the liver. On exposure to cold, however, when the animal was not merely exposed externally to temperature of 7° C, but was also breathing air at that temperature, the suprahepatic temperature fell by an average of 3·5° C, whilst in the liver it fell by an average of 2·5° C. The region between diaphragm and liver was thus 1·0° C cooler than the liver. Similar relationships were maintained even after adrenergic blockade. After administration of pentobarbitone sodium, however, although the diaphragm temperature still fell by an average of 3·5° C on exposure to cold, the liver temperature now fell practically equally, so that there was only a small temperature difference between liver and diaphragm. This is consistent with the concept of an inhibited liver losing heat by passive transfer through the diaphragm. The evidence is not complete, but supports the suggestion that pentobarbitone sodium is an inhibitor of liver function.

SUMMARY

1. Mean temperatures in tropical-bred conscious rats were found to be: liver, 39·3° C; mesentery (near portal vein), 39·1° C; lower abdomen, 38·5° C.

2. The evidence suggested that the intestines were an important producer of heat.

3. The effect of rapidly lowering the environmental temperature from 28·0 to 7° C, was investigated. In the conscious rat temperatures stabilized rapidly.

4. The ability to withstand exposure to cold was only slightly affected by ganglion blockade or by adrenalectomy, but a combination of those procedures or adrenergic blockade by Rogitine seriously impaired resistance to cold, and on exposure to cold temperature stabilization did not occur.

5. Liver blood flow remained steady in conscious or anaesthetized rats during exposure to cold.

6. Pentobarbitone sodium impaired resistance to cold and the evidence suggested that this was, in part, due to inhibition of liver function.

This work was aided by a grant from the Medical Research Council.

REFERENCES

BIRNIE, J. H. & GRAYSON, J. (1952). Observations on temperature distribution and liver blood flow in the rat. *J. Physiol.* **116**, 189–201.

FEDEROV, N. A. & SHUR, E. I. (1942). The role of the viscera in regulating the temperature of the body under physiological and pathological conditions. *Amer. J. Physiol.* **137**, 30–38.

FREGLY, M. J. (1953). Minimal exposures needed to acclimatize rats to cold. *Amer. J. Physiol.* **173**, 393–402.

GRAYSON, J. (1952). Internal calorimetry in the determination of thermal conductivity and blood flow. *J. Physiol.* **118**, 54–72.

LEWIS, T. (1930). Observations upon the reactions of the vessels of the human skin to cold. *Heart*, **15**, 177–208.