Our experiments confirm, as shown in Fig. 1, a difference between the sexes in susceptibility to the analgesic effect of morphine, female rats being less sensitive at the same body-weight—and consequently for the same total dose—than males.

Di Mattei's hypothesis[8] on the relations between the functions of certain vitamins and the pharmacological effects of some drugs suggests that morphine may affect in some way biological processes in which thiamine is involved.

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[1] Quastel, J. H., and Weatley, M. H., *Proc. Roy. Soc.*, B, **112**, 60 (1932).
[2] Santarato, R., *Boll. Soc. Ital. Biol. Sper.*, **29**, 626, 628, 630 (1953).
[3] Achor, L. B., and Geiling, E. M. K., *Arch. Int. Pharmacodyn.*, **105**, 313 (1956).
[4] Shideman, F. E., and Seevers, M. H., *J. Pharmacol.*, **71**, 383 (1941).
[5] Himmelsbach, C. K., *J. Pharmacol.*, **70**, 293 (1940). Himmelsbach, C. K., and Andrews, H. L., *ibid.*, **77**, 17 (1943).
[6] Fitzhugh, *J. Pharmacol.*, **67**, 423 (1939).
[7] Winter, C. A., and Flataker, L., *J. Pharmacol.*, **98**, 305 (1950).
[8] Di Mattei, P., "Attualità in tema di vitaminologia" (Cesalpino, 1942); "Questioni di attualità mediche e chirurgiche" (Pozzi, 1949); *La Riforma Medica*, **65**, 430 (1951); Atti Convegno sulle Vitamine, C.N.R. (1953).

Effect of Hypothermia on Death by Starvation

It is known that during the winter months some animals adjust themselves to unfavourable living conditions, particularly food shortage, by hibernation. This leads to a considerable lowering of the total metabolism and a drop in body temperature which enable the animals to survive the winter with a minimum consumption of nutrient.

Recently some very interesting substances have been prepared, for example, chlorpromazine, which produce an effect in some respects resembling hibernation. Hence the term 'artificial hibernation'. Chlorpromazine has been used with good results in psychiatry, surgery, pædiatrics and clinical states with a general hyper-reactivity of the patients.

We attempted to solve the problem, whether the effect of this substance can in some manner protect the animal from death from starvation, as this is, no doubt, the main purpose of hibernation in Nature.

The experiments were carried out on rats. We used 10 rats which had been fed on a standard diet (Larsen). They were then deprived of food while they had free access to water. Half the animals received chlorpromazine (Largactil Specia), 5 mgm./kgm. body-weight daily. The second group was used as control. Chlorpromazine, which lowered the body temperature of the experimental group by 3° C., caused a general apathy with a lowering of voluntary movements, but did not exert any influence on the time of survival (control group $6{\cdot}0 \pm 1{\cdot}4$, experimental group $6{\cdot}5 \pm 1{\cdot}73$ days; $P = 0{\cdot}7$) or on the loss of weight. The weight curves were the same in both groups. Nor was the excretion of nitrogenous substances much affected (control group 120 ± 27, experimental group 100 ± 12 mgm. nitrogen/24 hr./100 gm. weight; $P = 0{\cdot}2$) and ketone bodies (expressed as acetone) in the urine (control group $0{\cdot}18 \pm 0{\cdot}05$, experimental group $0{\cdot}19 \pm 0{\cdot}07$ mgm. ketone bodies/24 hr./100 gm. weight; $P = 0{\cdot}8$).

Apparently the drop of body-temperature under the influence of chlorpromazine was too small to protect the animals from death by starvation. We did not want to use larger doses of chlorpromazine for fear of pharmacological side-effects. Therefore in subsequent experiments we chose young rats (10 days old) because, as is well known from the literature[1–4], their body-temperature can easily be lowered to the environmental temperature. We used suckling rats from the same litter of which half (5 animals) were kept at an optimal temperature of 30° C., the second group at 20° C. Both groups of animals were taken from their mothers at the same time. The body-temperature of the animals kept at 20° C. dropped considerably within 15 min. and the rate of respiration decreased by as much as 40 per cent. In spite of this the group which survived in the colder environment was not protected against death by starvation. The time of survival at a temperature of 30° C. was $98 \pm 13{\cdot}6$ hr., at 20° C. $85 \pm 9{\cdot}9$ hr. ($P = 0{\cdot}2$). The total weight-loss as compared with the control group was, however, less than half (12·5 per cent loss of body-weight in animals kept at 20° C.; 34·3 per cent in animals kept at 30° C.; $P < 0{\cdot}01$). It is interesting that the relative composition of the carcase was, in both groups, practically the same. The animals kept at 30° C. had at the end of the starvation period a carcase composition of 80 per cent water, 20 per cent dry matter, 2·4 per cent nitrogen; the animals kept at 20° C. 82 per cent water, 18 per cent dry matter, 2·1 per cent nitrogen. During starvation, however, the control group kept at 30° C. lost 2·1 gm. more water (that is, 175 per cent more).

The animals kept at a temperature of 20° C. were pale, apathetic, with voluntary movements reduced, and a slow rate of respiration. The opposite was true of animals starving at 30° C.; they also had very strong sucking reflexes. It is interesting that as compared with the first group we noted a marked growth of fur in these animals during the starvation period.

The most probable explanation of our findings is that the hypothermia caused by chlorpromazine bears no relation to the reduction of the total energy metabolism. This is in agreement with the work of Ankermann and Jung[5], who showed that oxygen consumption in such animals is not reduced but actually has a tendency to rise. Chlorpromazine could cause a lowering of oxygen consumption and a reduction in metabolic rate if at the same time the body was cooled physically, thus lowering the temperature twice as much as in our experiments.

However, even experiments on young rats, where the reduction of body-temperature was as much as 10° C., did not protect the animals from death by starvation. This fact (independently confirmed at another laboratory: Faltová, E., and Konečná, V., personal communication) is very interesting from the point of view of the mechanism of death by starvation, since hypothermia protects animals, particularly young animals, from short-term stresses, such as anoxia, pain and poisons.

From our experiments, and those of other workers using 'artificial hibernation', it appears that the term 'hibernation' is not suitable.

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[1] Adolph, E. F., *Amer. J. Physiol.*, **155**, 366 (1948).
[2] Kabat, H., *Amer. J. Physiol.*, **150**, 588 (1940).
[3] Glaja and Markovič, cited by Čapek, D., "Fysiologie letce" (Praha, 1953).
[4] Symposium on "Problems of Physiology of the Pre-Weaning Period in Man and Mammals", sponsored by the Czechoslovak Academy of Sciences, Liblice, November 1956.
[5] Ankermann, H., and Jung, F., *Deutsch. Gesund.*, **11**, 667 (1956).