doses of pyrazole had an effect on livers of rats similar to that of frank hepatotoxic agents. Massive liver cell necrosis developing without symptoms of acute intoxication, when animals were kept on ethanol solutions as sole source of drinking fluid during pyrazole-induced inhibition of ADH, seems to argue against the assumption that necrosis was merely due to hypoxia or shock. At present it could not be decided whether ethanol only potentiated pyrazole toxicity. However, it seemed more likely that pyrazole-induced inhibition of ethanol metabolism increased ethanol toxicity resulting in liver cell damage of a severity hitherto not reported with conventional feeding techniques. This raises the question whether any hypothetical hepatotoxic action of ethanol may be distinct from its metabolic effect. In rats, with their high rate of ethanol oxidation, the use of a competitive ADH-inhibitor may be instrumental in producing liver lesions resembling those of 'acute alcoholic hepatitis' in man. This experimental design may prove to be of value in studying possible hepatotoxic properties of ethanol.

Zusammenfassung. Alkoholzufuhr bei partieller Hemmung der Alkoholdehydrogenase durch Pyrazol führte bei Ratten mit ihrem relativ hohen Alkoholumsatz in kurzer Zeit zu ausgedehnten Leberzellnekrosen, bei einigen Tieren auch zu bindegewebigen Reparations- und Umbauvorgängen.

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Respiratory Responses of the Conscious Dog to Severe Heat Stress

When the conscious sheep[1] and ox[2] are subjected to severe heat stress, body temperature, respiratory frequency and respiratory dead space ventilation all increase. Respiratory frequency ultimately reaches a maximum and then declines; during this second phase respiratory minute volume and alveolar ventilation further increase and respiratory alkalosis develops. During subsequent cooling there is a reversion to rapid shallow panting before respiration slowly returns to normal. The pattern is quite different in the anaesthetized dog[3,4]: there is no increase in respiratory frequency until there has been a considerable rise in body temperature (T_r) and the second phase is associated with a decrease in respiratory minute volume and alveolar ventilation which is not reversed by subsequent cooling; death from cardiovascular failure usually occurs[5]. Higgins and Iampietro[6] showed that alkalosis of venous blood can occur in the absence of hyperthermia in the conscious dog, but this study does not permit the complete resolution of the question whether the results obtained on the anaesthetized dog are wholly attributable to the effects of anaesthesia, or whether there are real species differences in the respiratory responses to heat stress. Further studies on the conscious dog which can be compared directly with those made on the sheep[1] and ox[2] have therefore been made.

Methods. 3 mongrel dogs weighing 15.3–16.7 kg were used. The right common carotid artery was brought to a subcutaneous position by previous surgery[1]. A polyethylene catheter (bore 1.0 mm, wall 0.25 mm) was introduced into the artery through a 13 s.w.g. hypodermic needle, after local infiltration with procaine. The animal then stood or lay quietly in a room at approximately 17 °C dry bulb/12 °C wet bulb temperature for about 1 h before entering an environment of 40/26 °C. After 20 min, humidity was rapidly raised to give a wet bulb temperature of 38 °C. The animal remained in this environment until T_r reached 42 °C, after which it was returned to the cool environment.

Rectal temperature, at a depth of 10 cm, and respiratory frequency were recorded throughout each experiment. Samples of arterial blood were taken at intervals, and a blood gas and pH electrode system (Radiometer, Copenhagen) was used to determine blood P_{CO_2} with an accuracy of $\pm$ 1 mm Hg, P_{O_2} with an accuracy of $\pm$ 2 mm Hg and pH with an accuracy of $\pm$ 0.005 units. Blood oxygen saturation (S_{O_2}) was measured to within 0.5% on an oximeter (American Optical Company) which had been calibrated with a standard spectrophotometric technique[7].

In an additional experiment on one dog tidal volume and respiratory minute volume were determined under the same experimental conditions using a pneumotachometer[8], but no blood samples were taken. In another experiment a dog was anaesthetized with sodium pentobarbitone (30 mg/kg i.v. + 1.5 mg/kg at 30 min intervals commencing 2 h after the initial dose) and was heated beneath an electric blanket while rectal temperature and respiratory frequency were recorded.

Results and discussion. The 3 conscious dogs responded similarly. The effects of severe heat stress on respiratory frequency, T_r, blood gases and blood pH are shown in Figure 1. Immediately upon exposure to the hot dry environment respiratory frequency increased 18-fold from 18 breaths/min to 340 breaths/min. When ambient humidity was raised there was a further increase in respiratory frequency which rose, within 10 min, to a peak rate of 410 breaths/min, before decreasing to 260 breaths/min.

From the record of thoracic movements and visual observations it was evident that when respiratory frequency rose, the depth of breathing decreased. However, when respiratory frequency fell at the onset of the second phase, the depth of breathing increased. This was confirmed by respiratory ventilation measurements on one of the dogs (Figure 2). Tidal volume decreased from 215 ml to 30 ml, and then increased to 203 ml. The result was a gradual increase in respiratory minute volume to 3 times the pre-exposure value at the peak of rapid shallow panting, and then a further increase to 11 times the pre-exposure level with slower deeper breathing. These changes are very similar to those seen in the

[1] J. R. S. Hales and M. E. D. Webster, J. Physiol. *190*, 241 (1967).
[2] J. R. S. Hales and J. D. Findlay, Respir. Physiol. *4*, 333 (1968).
[3] C. Albers, Pflügers Arch. ges. Physiol. *274*, 125 (1961).
[4] H. M. Frankel, J. P. Ellis and S. M. Cain, Am. J. Physiol. *205*, 733 (1963).
[5] C. Albers, personal communication.
[6] E. A. Higgins and P. F. Iampietro, Can. J. Physiol. Pharmac. *45*, 1 (1967).
[7] J. R. S. Hales, Ph. D. Thesis, University Glasgow (1968).
[8] D. L. Ingram and K. Legge, in course of preparation.

conscious sheep[1] and ox[2], except that in these species the increase in respiratory frequency is more gradual.

There was no change in the oxygen or acid-base status of the arterial blood in the conscious dog until rapid shallow panting was approaching its peak level. At the same time arterial P_{CO_2} fell to about 18 mm Hg and pH increased to about 7.59. The P_{O_2} and S_{O_2} were increased by about 32 mm Hg and 3% respectively. During the slower, deeper breathing P_{CO_2} fell to a final level of about 4 mm Hg about 20 min before the end of the heat exposure, while pH rose to 7.71 towards the end of the heat exposure. Again, this pattern of changes is very similar to that of the conscious sheep[1] and ox[2], although the sheep does not exhibit such marked changes in acid base balance during rapid shallow panting, and the final degree of respiratory alkalosis in the ox is not usually so great.

In contrast to the ox and sheep in which there was a correlation between respiratory activity and deep body temperature[9], none was found in the conscious dog. Rectal temperature usually remained unchanged during exposure to the hot dry environment, and then increased to 42 °C within 60 min of the humidity being raised; at the peak of rapid shallow panting it was 40.0, 39.5, 39.0 and 39.0 °C in the 4 experiments on conscious dogs and 41.5 °C in the one anaesthetized dog.

During cooling following severe heat stress, panting reverted to the rapid shallow form before respiration returned to normal, as occurs in the ox[10] and sheep[11] but not in anaesthetized dogs[3,5]. Our one experiment on an anaesthetized dog confirms the earlier reports[3,4] of a gradual onset of rapid shallow panting followed by an irreversible phase of slower deeper panting.

It may be concluded from these observations that the respiratory responses of the conscious dog to severe heat stress differ significantly from those of the anaesthetized dog, and are generally similar to those of the conscious sheep and ox[12,13].

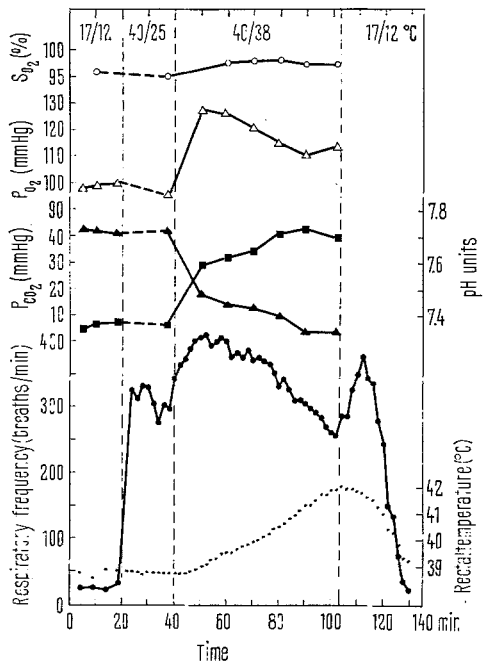

Fig. 1. The mean results from 3 conscious dogs of the effects of severe heat stress on respiratory frequency (●); arterial P_{CO_2} (▲); pH (■); P_{O_2} (△); S_{O_2} (○), and rectal temperature (·). The dry bulb/wet bulb temperatures to which the animals were exposed are indicated at the top. The vertical interrupted lines denote rapid changes in the ambient conditions.

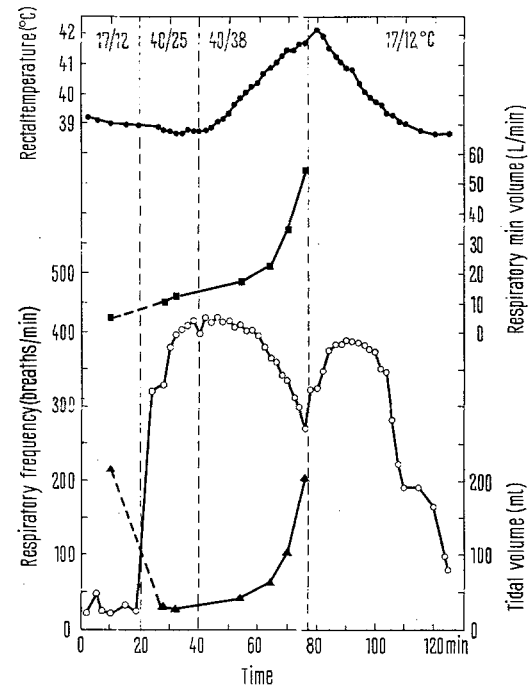

Fig. 2. The effect of severe heat stress on respiratory frequency (○); tidal volume (▲); respiratory minute volume (■), and rectal temperature (·) of a conscious dog.

Zusammenfassung. Atmungsverhalten unnarkotisierter Hunde bei starker thermischer Belastung: In erster Phase Erhöhung des Atemminutenvolumens durch Zunahme der Atemfrequenz bei niedrigem Atemzugsvolumen. In zweiter Phase weitere Zunahme des Atemminutenvolumens bei sinkender Atemfrequenz und erhöhtem Atemzugsvolumen. Entwicklung respiratorischer Alkalose. Spätere Senkung der Lufttemperatur auf 17 °C ergibt Wechsel des Atemtypus zu flachem hochfrequentem Hecheln der ersten Phase und dann Rückkehr zur normalen Ruheatmung.

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A.R.C. Institute of Animal Physiology, Babraham, Cambridge (England), 16 April 1969.

[9] J. D. FINDLAY and G. C. WHITTOW, J. Physiol. *186*, 333 (1966).
[10] W. R. BEAKLEY and J. D. FINDLAY, J. agric. Sci., Camb. *45*, 452 (1955).
[11] J. R. S. HALES, J. comp. Biochem. Physiol., in press (1969).
[12] We thank Messrs A. J. BARTON, M. MASKREY and D. T. NEWMAN for their technical assistance.
[13] This work was carried out while J.R.S.H. was in receipt of a scholarship from C.S.I.R.O., Australia.
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