ambient temperature of $0 \pm 2^{\circ}$C for three hours. During exposure to cold, body temperature increased and was associated with vasoconstriction, a crouched posture and shivering. Levels of cAMP in c.s.f. removed during and after this period were not significantly different ($P > 0.2$) from control levels (ambient temperature $25 \pm 1^{\circ}$C).

Exposure to an ambient temperature of $45 \pm 1^{\circ}$C for 3.5 h caused the body temperature of the cats to rise $2.45 \pm 0.30^{\circ}$C and was associated with vasodilatation, panting and stretching out. Upon cessation of heat exposure body temperature fell rapidly to control levels. Levels of cAMP in c.s.f. during and after heat stress were not significantly different ($P > 0.1$) from control.

cAMP (0.1-10 mg/kg) injected intravenously in cats at an ambient temperature of $22 \pm 2^{\circ}$C caused a dose-related, rapid increase in the amount of cAMP assayed in c.s.f. High doses (5 mg and 10 mg/kg) of cAMP, but not lower doses (0.1 mg and 1 mg/kg), produced a significant ($P < 0.01$) fall in rectal temperature, which began 2-3 min after injection and reached a maximum in about 18 minutes. The hypothermia was associated with ear skin vasodilatation, and in one animal in response to cAMP 10 mg/kg, polypnoea and sweating from the paw pads.

Intravenous injections of ^{3}H-cAMP were followed by a rapid rise in ^{3}H-cAMP levels in the c.s.f. showing that the exogenous nucleotide was passing from the blood into the c.s.f.

The level of cAMP in c.s.f. may therefore be raised as a result of increased levels of cAMP in the blood; as these results show, the nucleotide rapidly enters c.s.f. from the blood. The raised levels of cAMP recently reported following i.v. bacterial pyrogen could possibly result from raised levels of cAMP released peripherally by the pyrogen. The raised levels of cAMP reported during bacterial pyrogen-induced fever are not, however, considered a consequence of either raised body temperature or active thermoregulatory processes.

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Cyclic AMP in developing chick brain: changes with ischaemia and catecholamine administration

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Cyclic AMP has been implicated in the functioning of the central nervous system, and there is evidence indicating that cyclic nucleotides are involved in the control of cell growth and differentiation (for review, see Drummond, 1973). The concentration of cyclic AMP in rat brain has been reported to increase throughout development (Schmidt, Palmer, Dettbaru & Robison, 1970; Ebadi, Weiss & Costa, 1971), but the method of sacrifice used in these studies does not eliminate rapid post-mortem changes in the nucleotide (Nahorski & Rogers, 1973).

We have measured the concentration of cyclic AMP in the cerebral hemispheres of chicks during their neonatal development using a method whereby brain tissue is removed and frozen by a freeze-blowing technique which largely eliminates post-mortem changes (Nahorski & Rogers, 1973). Cyclic AMP was assayed by the protein binding saturation method of Brown, Albano, Ekins, Sgherzi & Tampion (1971). The cyclic AMP content of freeze blown chick cerebral hemispheres was found to decrease during neonatal development, from 12.5 ± 0.8 p moles/mg protein in one day old chicks to 3.0 ± 0.01 p moles/mg protein in 28 day old chickens. However, in chicks killed by decapitation there was a rapid increase in cerebral cyclic AMP. This post-mortem rise in the

nucleotide concentration increased with age. One minute of ischaemia induced an increase of 23.5 p moles/mg protein in the one day old chick and 48 p moles/mg protein in the 28 day old bird compared with the appropriate controls. It is possible, therefore, that the discrepancy between the developmental changes in cyclic AMP obtained in the present study and those obtained in the rat by Schmidt *et al.* (1970) may be due to age dependent post-mortem hypoxic increases in brain cyclic AMP.

In the neonate chick with its immature blood-brain barrier, the systemic administration of β-adrenoceptor agonists has been shown to increase the concentration of cyclic AMP in chick cerebral hemispheres *in vivo* (Edwards, Nahorski & Rogers, 1974). In the present study chicks of varying ages were injected intravenously with isoprenaline (5 μmoles/kg) and were killed by freeze-blowing 3 min later. The isoprenaline-induced increase in cyclic AMP was maximal in three day old chicks (+19.7 p moles/mg protein) but diminished with age (+3.3 p moles/mg protein in 28 day old birds).

^{3}H-noradrenaline was given intravenously to chicks aged 2-28 days, and its penetration into the brain was determined. Brain levels of ^{3}H-noradrenaline at 28 days of age were only 19% of those at two days of age. It is probable, therefore, that the decrease in the *in vivo* cyclic AMP response to isoprenaline with age is due to the development of a blood-brain barrier to catecholamines rather than a change in receptor sensitivity. *In vitro* studies to further substantiate these results are now in progress.

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Antinociceptive activity in mice after central injections of α- and β-adrenoceptor antagonists

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Recent studies have demonstrated that narcotic agonist and partial agonist analgesic agents interact in a specific way with certain putative central transmitters: thus, the intracerebroventricular (ICV) injection of 5-hydroxytryptamine (5-HT) potentiates whilst the ICV injection of noradrenaline (NA) attenuates the antinociceptive activity of these agents in experimental animals (Sewell & Spencer, 1974). The present study sets out to characterize more fully the nature of this attenuation by ICV-administered NA.

Nociceptive sensitivity was measured repeatedly at fixed intervals in ICI-derived albino mice weighing 18-22 g, using the tail-immersion method described in the earlier report. It had already been demonstrated that the centrally-acting α-sympathomimetic agent clonidine possessed antinociceptive activity in experimental animals (Schmitt, Le Douarec & Petillot, 1974), and this has been confirmed by the present authors using the tail-immersion test in mice. However, when clonidine was given by ICV injection (0.5 μg/animal), it possessed only marginal antinociceptive activity, and furthermore substantially attenuated the antinociceptive effect of morphine (3 mg/kg) when given concurrently. The α-adrenergic antagonist phentolamine (10 μg/animal, ICV) exhibited antinociceptive activity when given alone and significantly potentiated the activity of a subcutaneously administered concurrent dose of morphine (3 mg/kg) or pentazocine (15 mg/kg). The antinociceptive activity of subcutaneously