individual cells. This latter problem has to some extent been overcome by the systematic isolation and analysis of a variety of neuroblastoma of clonal origin (Amano, Richelson and Nirenberg, *Proc. US Nat. Acad. Sci.*, **69**, 258 ; 1972). Some clones give rise to cells containing extremely high activities of the enzyme tyrosine hydroxylase, and one of these "adrenergic clones" has been used by Richelson (*Nature New Biology*, **242**, 175 ; 1973) to examine the control of the synthesis of the enzyme tyrosine hydroxylase.

Richelson confirms the previous finding (in a similar but less active neuroblastoma preparation) of Waymire, Weiner and Prasad (*Proc. US Nat. Acad. Sci.*, **69**, 2241 ; 1972) that the addition of dibutyryl cyclic AMP causes approximately a doubling in the activity of tyrosine hydroxylase. The new study shows, furthermore, that this change in enzymatic activity represents both an increase in the specific activity of the enzyme (per milligram protein) and an increase in the total amount of enzymatic activity per cell. This is an important point, because Richelson also confirms (as reported by Waymire *et al.*, 1972) that sodium butyrate — a possible metabolic product from dibutyryl cyclic AMP — causes an increase in the amount of tyrosine hydroxylase per cell, but not in its specific activity.

Sodium butyrate seems to inhibit cell division. In the normal growth of neuroblastoma cells in tissue culture, formation of the enzyme occurs largely after the log phase of growth is completed ; by arresting cell division butyrate seems merely to accelerate the normal processes of biochemical differentiation occurring in the cultured cells. When cells were cultured with reduced amounts of foetal calf serum, so that cell division was not encouraged, butyrate no longer had any effects, although dibutyryl cyclic AMP was still effective. The actions of dibutyryl cyclic AMP were enhanced by the phosphodiesterase inhibitor theophylline. Prostaglandin E_1, however, which has been reported to increase the concentration of cyclic AMP in neuroblastoma cells, did not cause any marked increase in tyrosine hydroxylase activity. The results, nevertheless, strongly suggest that cyclic AMP may play a part in the biochemical differentiation of neuroblastoma cells, and, by inference, of adrenergic neurones. Addition of dibutyryl cyclic AMP has also been shown to influence other aspects of the morphological and biochemical specialization of neuroblastoma cells (Prasad and Hsie, *Nature New Biology*, **233**, 141 ; 1971 ; Furmanski, Silverman and Lubin, *Nature*, **233**, 413 ; 1971).

The implications of Richelson's findings in neuroblastoma cultures have been supported by recent results obtained with normal adrenergic cells. Addition of dibutyryl cyclic AMP to organ-cultured mouse and rat sympathetic ganglia leads to increased synthesis of the enzymes tyrosine hydroxylase and dopamine-β-hydroxylase in the adrenergic neurones of these ganglia (Mackay and Iversen, *Brain Res.*, **48**, 424 ; 1972 ; Keen and McClean, *Arch. Pharmacol.*, NS, **275**, 465 ; 1972). In such isolated ganglia, the stimulation of tyrosine hydroxylase activity by nerve activity *in vivo* can be simulated by the addition of substances such as potassium chloride that cause a depolarization of the adrenergic neurones. These effects are enhanced by theophylline, suggesting again an involvement of the cyclic AMP system in mediating the control of enzyme synthesis by depolarizing stimuli. Such an involvement is also supported by the finding (Guidotti and Costa, *Science*, **179**, 902 ; 1973) that conditions leading to increased tyrosine hydroxylase activity in rat adrenal medullary chromaffin cells *in vivo* are associated with an increase in the concentration of cyclic AMP in such cells. The phosphodiesterase inhibitor aminophylline also promotes an increase in the cyclic AMP content and in tyrosine hydroxylase activity in these cells.

The biological ramifications of the adenylate cyclase-cyclic AMP control system know no bounds. A role in controlling neuronal plasticity, however, is at least a relatively novel regulatory function for this ubiquitous messenger substance.

From our Neuropharmacology Correspondent

GROOMING MOVEMENTS

Endogenous Control

from our Animal Behaviour Correspondent

DURING the past ten years, considerable interest has centred on the effects that various sorts of feedback from an animal's own movements or sounds have on the subsequent development of complex species-specific patterns of behaviour. White-crowned sparrows, for example, need to hear the sound of their own voices if they are to develop the proper song characteristic of their species. When white-crowned fledglings, which have been exposed to their species song, are deafened before they themselves have started singing, they subsequently produce highly abnormal songs (Konishi, *Z. Tierpsychol.*, **22**, 770; 1965). They thus seem to need to hear

Reverse Transcriptase of Chick Cells

IN *Nature New Biology* next Wednesday (April 18) Kang and Temin report new data which add support to their claim to have detected in chick embryo cells an RNA-dependent DNA polymerase ; in other words a reverse transcriptase, which is biochemically and serologically distinct from the reverse transcriptase present in avian RNA tumour viruses. Last year Kang and Temin reported (*Proc. US Nat. Acad. Sci.*, **69**, 1550 ; 1972) that chick cells contain an endogenous reverse transcriptase associated with an endogenous RNA template. They showed that this activity is sensitive to RNase, resistant to DNase, partially resistant to actinomycin D and makes a DNA complementary to the associated RNA. They failed, however, in their initial attempts to isolate a RNA/DNA hybrid intermediate made by this chick endogenous reverse transcriptase.

By varying slightly the method of isolating this endogenous reverse transcriptase activity, Kang and Temin have now succeeded in obtaining preparations which *in vitro* synthesize DNA and give rise to an RNA/DNA hybrid, the RNA moiety of which is sensitive to RNase and alkali and can be heat denatured. Furthermore, they obtained evidence which suggests that the DNA chain of the hybrid may be covalently linked to an RNA primer molecule. These properties of the RNA/DNA hybrid molecules made by this activity are reminiscent of the RNA/DNA hybrids made at early times by reverse transcriptase of tumour viruses, but the endogenous enzyme of chick cells and the enzyme in avian RNA tumour virus particles are different molecules. As Kang and Temin say, these data "suggest that endogenous RNA-directed DNA polymerase activity is not unique to viruses, and virus-infected or tumour cells". What role the endogenous reverse transcriptase of chick cells plays remains a fascinating question.