CYCLIC AMP AND A POSSIBLE ANIMAL MODEL OF RECEPTOR SUPERSENSITIVITY

D. ECCLESTON
MRC Brain Metabolism Unit, 1 George Square, Edinburgh, Scotland.

CONVENTIONAL techniques for investigating aminergic function in man: namely the estimation of amine metabolites in C.S.F. have suggested that factors other than transmitter output should be considered in affective illness. Levels of 5HIAA have been found to be low in unipolar depressed patients but normal in bipolar depression (MRC BRAIN METABOLISM UNIT, 1972). These workers also suggested that clinical observations of changes in the facial dyskinesias with the phase of manic depressive illness may be related to changes in post synaptic receptor supersensitivity. The demonstration that receptor supersensitivity in brain can be linked to adenyl cyclase activity is, then, important. In the animal model described this is indicated.

The locus coeruleus (LC) is a bilateral noradrenergic nucleus supplying cortex almost ipselaterally (UNGERSTEDT, 1971). The production of supersensitivity in dopaminergic receptors has been established by lesions of the cell bodies in the substantia nigra (UNGERSTEDT, 1971). Similar supersensitivity in the noradrenergic system should follow lesions of one LC and this should be unilateral. In these experiments electrolytic lesions are made in one LC and the animals allowed to recover. Subsequently cortical slices are prepared and cyclic AMP production measured by the

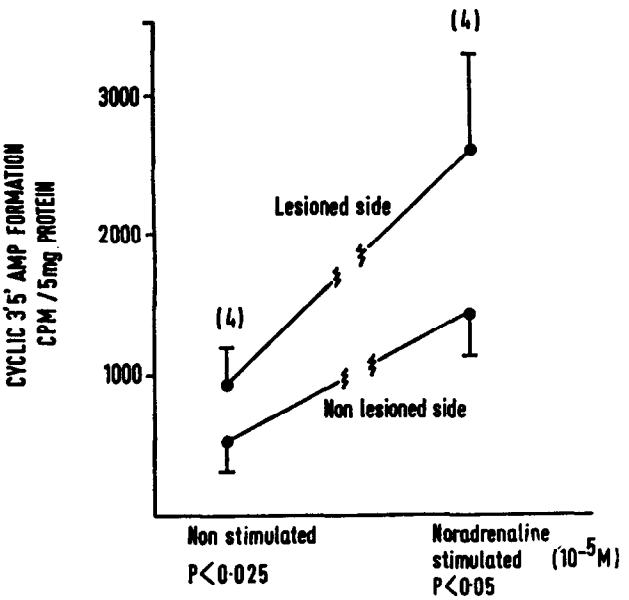

FIG. 1.—Formation of ^{14}C cyclic AMP from ^{14}C adenine in animals with unilateral lesions of locus coeruleus when no NA added to incubation medium or when incubated with 10^{-5} M NA. (paired *t*-test).

method of SHIMIZU *et al.* (1969). In these experiments two points arise: firstly there is a significantly increased cyclic production on the side of the lesion both in unstimulated slices and in response to NA stimulation compared with slices prepared from the unlesioned side of the animal (Fig. 1), and secondly this increased response to NA develops over at least 4 weeks.

Perhaps the efforts now being directed to determine adenyl cyclase function in man—more specifically in brain, are important. This study which shows that the development of changes is over some weeks may give us a clue to the paradoxically slow response to the cyclic antidepressants and perhaps also to the long term phasic nature of affective illness.

REFERENCES

MRC BRAIN METABOLISM UNIT (1972) *Lancet* **ii,** 573–577.
SHIMIZU H., CREVELING C. R. and DALY J. (1970) *Proc. Natl Acad. Sci.* **65,** 1033–1040.
UNGERSTEDT U. (1971) *Acta Physiol. Scand.* suppl. 367.