adequate for the sRNA methylation of the growing fetal cell, if methylation is mandatory for normal protein synthesis. Perhaps the fetal cells have the ability to obtain methyl groups from another source – either maternal or via another pathway. It is quite conceivable that the sRNA methylase(s) of fetal liver is more diverse in its ability to methylate different sites on the sRNA molecule. Thus the increase in potential nucleotide sites is reflected in the increased efficiency and rate of methylation. The average sRNA molecule from embryonic liver may have more methyl groups than sRNA from adult liver. SIMON and GLASKY[8] have recently reported an increase in sRNA methylase activity in developing mammalian brain. RODEH et al.[9] showed that no increase in extent of methylation occurred using extracts of newborn rat liver. Our studies on the extent of methylation using fetal mouse liver as the source of sRNA methylase have shown a multifold increase in extent of methylation of *E. coli* sRNA by fetal liver preparations as compared with the adult liver fraction.

With the use of SAM-$^{14}CH_3$ it has been determined that fetal liver has large amounts of sRNA methylase activity in contrast to adult liver.

Résumé. Utilisant SAM-$^{14}CH_3$ il a été démontré que le foie foetal a plus d'activité de sRNA methylase que le foie adulte.

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The Jackson Laboratory, Bar Harbor (Maine 04609, USA), 3rd March 1967.

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The Influence of Antidepressant Drugs on Akinesia Produced in Mice by Intracisternally Administered Noradrenaline, Dopamine and Noradnamine

We have previously proposed that malfunction of catechol-O-methyl transferase (COMT) could be the biochemical disturbance responsible for endogenous depressive reactions, and have suggested an in vivo synthetic route whereby the excess deaminated metabolites of noradrenaline likely to occur under these conditions could be converted to noradnamine, a dibenzocycloheptatriene[1]. Subsequently it was pointed out that dopamine might also be able to produce this postulated depressive catabolite[2].

Reserpine induced sedation is antagonized by antidepressant drugs of both the monoamine oxidase (MAO) inhibitory and the iminodibenzyl groups[3–6], yet paradoxically catecholamines themselves cause loss of spontaneous motor activity when administered centrally to animals[7–9]. Since reserpine causes depletion of brain catecholamines predominantly via MAO[10] it seemed possible that the akinesia induced by reserpine and by the catecholamines could be mediated via a common deaminated metabolite such as our postulated noradnamine. If this were so, then noradrenaline, dopamine and noradnamine should all produce akinesia antagonizable by iminodibenzyl antidepressants; on the other hand only the loss of activity resulting from injections of noradrenaline and dopamine should be antagonized by MAO inhibitors. The present study is a test of this hypothesis.

Male albino mice (18–22 g) were placed individually into a corner of 1 of 4 boxes (55 × 33 cm) marked out into areas 11 × 11 cm and the number of lines the mice crossed in 5 min was recorded. Each mouse was then placed in a second box for 5 min and the mean of the 2 counts was used as the control activity. The mice were then given the drug under test by intracisternal injection under ether anaesthesia[11], and after 15 min rest in a neutral cage were again tested for periods of 5 min in the third and fourth boxes. The mean of these 2 counts gave the experimental activity of the mouse. The experiments were repeated in the presence of a MAO inhibitor (nialamide, 50 mg/kg, s.c. 18 h before the experiment) and a tricyclic antidepressant (amitriptyline, 3 × 50 mg/kg, orally 36, 24 and 12 h before the experiment).

Results were measured for each mouse as a percentage change in activity following the intracisternal injection and for each dose level the mean percentage change of 10 mice was calculated. These mean figures were plotted against the logarithm of the dose of injected amine and the calculated regression lines were subjected to a statistical analysis of variance.

The results are summarized in the Table. Pretreatment with amitriptyline, but not with nialamide, caused a highly significant ($p = 0.0001$) 33.75% reduction in activity.

All 3 amines induced akinesia in mice, but noradnamine was only half as potent as the equipotent dopamine and noradrenaline; in each case the loss of spontaneous motor activity was antagonized by both amitriptyline and nialamide. It must therefore be concluded that catecholamine induced akinesia in mice is not mediated via the formation of noradnamine. Several points of interest arise from our observations however. For example, the paradox that akinesia is produced both by the cate-

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Percentage inhibition of spontaneous motor activity induced by intra-cisternal injections of noradrenaline, dopamine and noradnamine and its antagonism by nialamide and amitriptyline

Agonist (μg/mouse)	Pretreatment		
	None	Nialamide	Amitriptyline
Noradrenaline		[b]	[b]
2.5	58.76 (2/10)	25.36 (1/10)	53.23 (3/10)
5	65.67 (4/10)	57.95 (3/10)	58.22 (3/10)
10	82.72 (8/10)	75.81 (5/10)	56.72 (3/10)
Dopamine		[a]	[b]
2.5	63.35 (2/10)	45.09 (0/10)	44.99 (2/10)
5	65.53 (5/10)	55.72 (4/10)	50.28 (1/10)
10	76.65 (6/10)	61.77 (4/10)	53.03 (2/10)
Noradnamine		[a]	[a]
5	51.37 (2/10)	25.83 (1/10)	37.81 (1/10)
10	68.15 (4/10)	56.98 (5/10)	62.95 (2/10)
20	84.52 (8/10)	70.61 (6/10)	71.63 (6/10)
Control counts	160.34 ± 3.14 (135)	155.94 ± 5.55 (90)	106.22 ± 4.03 (90)[c]

Figures in parenthesis indicate the number of mice in each group passing a quantal test for inhibition based on 72.58% inhibition and above being positive. This percentage is twice the inhibition seen with control mice following etherization and intracisternal injections of saline. Etherization alone caused 16.55% (0/10) inhibition while in the absence of any treatment only 4.42% inhibition was evident between initial and test counts. [a] p, 0.05; [b] p, 0.01, for differences between regression lines that had passed tests for linearity, parallelism and regression. Mean control actual counts (± standard errors) are given at the bottom of the Table. In these cases the figures in parenthesis are the number of observations; [c] p, 0.0001.

cholamines and by reserpine (which depletes the brain of catecholamines) is now extended in that the loss of spontaneous motor activity in both instances is antagonized by the antidepressive drugs. Admittedly reserpine also causes loss of brain 5-hydroxytryptamine (5-HT)[12] but this is presumably unrelated to the loss of spontaneous motor activity since in contrast to the catecholamine precursor dihydroxyphenylalanine (dopa), the administration of the 5-HT precursor 5-hydroxytryptophan (5-HTP) does not antagonize reserpine induced akinesia[13]. Furthermore, since reserpine has been shown to result in the loss of catecholamines as deaminated metabolites[10] the effects of reserpine cannot be considered to result from the release of active amine.

By contrast these same observations could be interpreted as implicating deamination in the loss of spontaneous motor activity induced by both reserpine and the catecholamines. The antagonism of akinesia by the tricyclic antidepressants is open to the same interpretation in that they are known to prevent the uptake of catecholamines into the neurones[10,14] where MAO is located. BRITTAIN[15] has recently reported antagonism of the hypothermic effects of intracerebroventricular injections of noradrenaline by imipramine-like antidepressants, although the use of monoamine oxidase inhibitors resulted in a potentiation of the effects of noradrenaline. From a close investigation of the Table it is obvious that significant antagonism of amine induced akinesia by nialamide and amitriptyline was not obtained at all dose levels, but in no experiment was the loss of spontaneous motor activity potentiated. Perhaps hypothermia does not correlate with akinesia, or perhaps the differences may be explained by the different routes of injection.

The experiments are being repeated using more refined apparatus and extending the parameters measured to include most of the more usual tests for drugs acting on the central nervous system. For the time being, however, our results are not at variance with the suggestion that MAO is involved in the akinesia produced by intracisternally administered catecholamines. The significance of these findings in relation to mood changes in man must await the results of further studies but from measurements of catecholamine metabolites in urine quoted in existing literature[16,17] there is already some evidence of excessive deamination and diminished O-methylation being associated with depression. By contrast schizophrenia appears to be associated with increased activity of COMT and decreased activity of MAO[18]. In this context it is interesting to note that the symptoms presented by these 2 conditions might be considered to represent opposite ends of a mental spectrum.

Zusammenfassung. Die Hemmung psychopharmakologischer Noradrenalin-, Dopamin- und Noradnaminwirkungen durch Antidepressiva wird beschrieben, wobei die beiden verwendeten Antagonisten bestimmt verschiedene Wirkungsmechanismen haben.

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