must have been performed with an isomeric mixture; the present results suggest that it was predominantly *meso*-DMM containing 5–10% of (±)-DMM. Secondly, as the action of DMM on a variety of biological parameters is known to parallel that of much larger doses of Myleran, and as it has been assumed[2] that these studies were carried out with the *meso*-isomer, it could be that the compounds used were similarly 'impure' and contained varying amounts of (±)-DMM. Therefore, it would be interesting to re-investigate these actions of DMM and, if both isomers are active, to see if either a similar type of synergism or a decrease in toxicity[12] occurs. A more detailed histological examination of the effects of the 'pure' isomers and the 50% mixture on the rat testis is at present being investigated.

Table II. Effects of the isomers of dimethylmyleran on the fertility of male quail (*Coturnix coturnix japonica*).

| Dose (i.p.) | % of isomers | | No. of days |
|---|---|---|---|
| | *meso*- | (±)- | of sterility |
| 10[a] | 0 | 100 | 0 |
| 10[a] | 100 | 0 | 2 |
| 10 | 50 | 50 | 4 |
| 20[a] | 50 | 50 | 23[b] |

Sterility, calculated from day 25 post-administration[9], was assessed as previously described[11]. [a] maximum tolerated doses. [b] of four test birds, two were permanently sterile.

*Zusammenfassung.* Als Antifertilitätsmittel haben das *meso*-Isomer und die (±)-Isomere von Dimethylmyleran eine synergistische Wirkung auf die Spermatogenese von Ratten. Bei Mäusen und Wachteln hat ein 50%iges Gemisch der Isomere eine niedrigere Toxizität als die einzelnen Isomere, was bei höherer Dosis des Gemisches zu längerdauernder Sterilität führt.

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## Mechanism of Action of CDP-Choline in Parkinsonism

CDP-choline (cytidine diphosphate choline), which had been developed as a therapeutic for consciousness disturbance, was found to have an effect in Parkinson's syndrome. A total of 102 patients with parkinsonism were treated with the drug at sixteen medical institutions up to 1971[1,2]. The treatment with CDP-choline yielded effectiveness rate (per cent of cases improved) of 80% approx. The therapeutic effect of the drug in parkinsonism is generally comparable to that of L-DOPA, i.e. prominent effect on bradykinesia, less but significant effect on rigidity and rather modest effect for tremor. Improvement in speech, gait and writing is also conspicuous. The dosage of CDP-choline administration was between 300–500 mg q.d. by the i.v. or i.m. route.

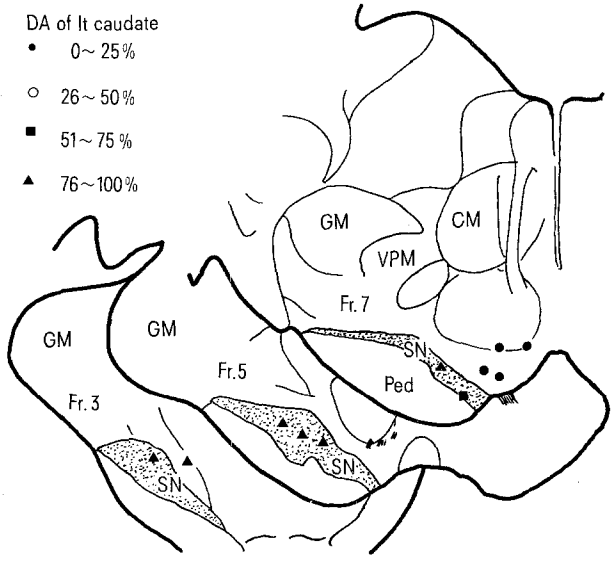


Fig. 1. Interrelation between the site of destruction of substantia nigra and the rate of dopamine diminution. Destruction of the central and caudal regions did not cause significant diminution of dopamine whereas destruction of the rostral region, especially the region medial to it, brings about a marked depletion of dopamine.

CDP-choline is devoid of anticholinergic action and its therapeutic efficacy in consciousness disturbance is attributable to its ability to ameliorate phospholipid metabolism with consequent improvement of deteriorated function of neurons[3–5].

Dopamine in the corpus striatum is originated in the homolateral substantia nigra, and parkinsonism is derived from that dopamine deficiency[6]. The mode of effectiveness of CDP-choline resembles that of L-DOPA, therefore the mechanism of action of CDP-choline in parkinsonism might be related to the activity of the drug to enhance the production of dopamine in the substantia nigra and to improve the deteriorated axonal flow of dopamine from the substantia nigra into the striatum. To clarify this possibility, the following experiments were performed.

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*Method.* 49 adult cats (from 2.0 to 3.5 kg), anesthetized by i.p. Nembutal of 25 mg/kg, were used.

The preliminary experiments demonstrated[7] that practically uniform levels of dopamine in the right and the left caudate in 9 untreated cats, and that the caudate dopamine depletion consequent to destruction of the substantia nigra in 17 cats is affected by the site of destruction rather than the duration after operation; the destruction of the rostromedial part of the substantia nigra provides maximal diminution (Figure 1).

In 23 cats, arranged in pairs, the substantia nigra on one side was destroyed by radio-frequency current which produced lesion of ca. 2 mm in diameter with consequent diminution of dopamine in the homolateral caudate nucleus[6]. The target is either of midportion or the rostromedial portion or both of the midportion and rostral portion of the substantia nigra.

One in each pair was then given CDP-choline daily in an i.m. dose of 200 mg, and the other in each pair, a comparable volume of saline injected by same route for 2 to 5 weeks. After that, the cats were sacrificed for dopamine assay. The brain was cut at frontal 12 mm from the aural orifice; the anterior half was taken out to extract the bilateral caudates, which was frozen immediately in liquid nitrogen whereas the remaining portion of the brain, which was utilized for confirmation of the site of destruction and for histological examination, was perfused with 10% formalin.

Tissue dopamine assays were performed by the method described by ANSELL and BEESON[7]. As the parameter for comparison between the treated and the control group, the rate in percentage of dopamine depletion of caudate on the treated side comparing with the non-treated side i.e., (left caudate dopamine/right caudate dopamine) $\times 100$ was used.

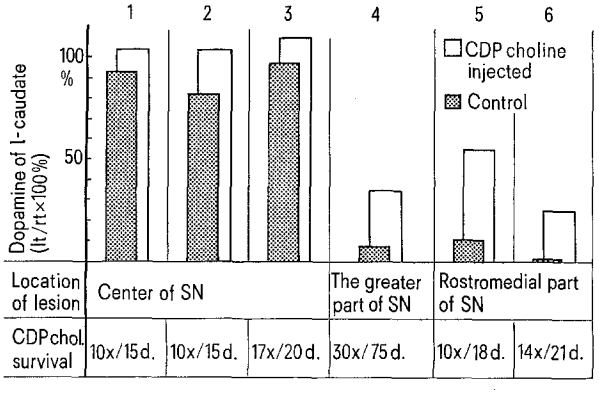


Fig. 2. Interrelation between CDP-choline and dopamine in the caudate. To cats with dopamine depletion in the caudate by destruction of the substantia nigra, CDP-choline was injected i.m. in a dose of 200 mg daily into one in each pair and saline into the other in each pair, respectively. CDP-chol./Survival: duration of CDP-choline administration and the number of days between destruction of the substantia nigra and extraction of the caudate. 3 cats were used in groups 2 and 3, and those with disadvantageous data were adopted. It can be seen from the chart that cats treated with CDP-choline showed higher dopamine levels than the untreated controls.

*Results.* Figure 2 illustrates the results of the experiments. 1. 3 pairs out of 4 pairs of cats revealed destruction of the midportion of the substantia nigra. Controls in these pairs displayed diminution rates of 82, 93 and 98%; thus only a slight depletion. CDP-choline treated cats, on the other hand, showed rates of 104, 104, and 108% respectively; thus the dopamine levels were consistently higher than those in the untreated controls. It follows that the treated animals showed no diminution of dopamine at all, whereas the dopamine level diminished slightly in untreated cats.

2. There were 2 pairs of drop-outs among the 3 with extensive destruction of the midportion and rostral portion of the substantia nigra, and the experiment was successful in the remaining pair. The rate of diminution shown by the control in this pair was 8%, while the treated cat displayed a rate of 36.7%, indicating a dopamine level approximately 4 times as high as that in the untreated control.

3. There were 2 successful pairs out of 3 pairs with destruction of the medial portion of the rostral end of the substantia nigra, in which the experiment was successful. The control cat in 1 pair (No. 5) showed a dopamine diminution rate of 12%, whilst the treated one in this pair displayed a rate of 57%, about 5 times as high. In the other pair (No. 6), the rate shown by the control was 0% (viz. disappearance of dopamine in the caudate on the side of destruction) and that by the treated cat was 27%; hence an obvious difference.

4. Histological examination: Degeneration of nerve cells of the pars compacta of substantia nigra in parallel with the diminution of caudate dopamine concentration was in evidence. The cats treated with CDP-choline showed milder degenreation and loss of nerve cells in the substantia nigra than the untreated cats did.

*Conclusion.* CDP-choline is proved to exert a significant ($0.001 < P < 0.01$) protective effect against diminution of dopamine in the caudate derived from ipsilateral destruction of the substantia nigra. The mechanism might be postulated that phospholipid metabolism of injured nerve cells in the substantia nigra and nigrostriatal tract is improved by CDP-choline and, as a result, the production of dopamine is augmented and the transporting activity is also ameliorated.

*Zusammenfassung.* Es ist anzunehmen, dass CDP-Cholin (Cytidin-Diphosphat-Cholin) auf Verminderung von Dopamin im Nucleus caudatus einen signifikanten ($0.001 < p < 0.01$) Abwehreffekt ausübt, was durch homolaterale Destruktion der Substantia nigra verursacht wird.

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## Selective Calcium-Alkali Metal Exchange in a Synaptic Membrane Protein[1]

It is well-recognized that bioelectric phenomena are associated with differential fluxes of alkali metal ions across permselective membranes; and although a great deal is known about the kinetics of the ionic fluxes, little is known of the chemical architecture of the membrane, particularly concerning its permselectivity. The problem has been investigated using a variety of materials ranging from artificial ion exchange systems to intact muscle and nerve[2,3]. Although such studies have yielded valuable information on the selectivity sequences of