Haloperidol-Induced Dyskinesias in the Monkey

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SUMMARY: Haloperidol (0.25 mg/kg i.m.) was injected daily for 6 months in six normal monkeys. Over a 24 hour period, the following symptoms could be observed: akathisia, circling, akinesia, choreoathetoid and dystonic movements, oro-facial dyskinesias and postural tremor with or without harmaline. Six months after cessation of haloperidol, harmaline-induced postural tremor could still be observed in all animals and oro-facial abnormal movements in one monkey. The neuropathologic study of the experimental material did not disclose any alteration of the central nervous system.

RESULTS (Table 1)

All monkeys repeatedly displayed certain common features after each injection. Initially these consisted of excitatory or restless behavior, characterized by exploratory behavior and vocalizations and attempts to free themselves when sitting in a restrain-
ticularly conspicuous during the peak of akinesia, between 1 and 6 hrs. after the injection. First, there was rapid flexion and extension of the fingers, then torsion of the limbs and finally generalized dystonia involving the trunk and limbs. The latter signs appeared in several forms including crucifixion (Baruk et al., 1956) and walking with the head on the floor and the posterior limbs extended (Deneau et al., 1969). When the upper limbs were free, we observed repetitive movements of the fingers and hand reminiscent of athetosis (see film strip, fig. 1) and occasionally chewing and tongue protrusion. These abnormal movements were not abolished by DL-alpha-methyl-tyrosine (150mg/kg i.p.) and they could not be triggered by apomorphine (1mg/kg i.m.). All abnormal movements except those involving the oral region could be abolished by benztropine mesylate (0.5mg/kg i.m.). Tremor, although diminished, was not completely abolished.

Monkey H-94 developed, after 2 months of treatment, rapid chewing movements and tongue protrusion. The movements were very similar to the tardive oral dyskinesias often described in human patients as a consequence of chronic neuroleptic treatment. They were not diminished 6 months after treatment with haloperidol had stopped. They were not modified either by DL-alpha-methyl-tyrosine (150mg/kg i.p.) or by benztropine mesylate (0.5mg/kg i.m.).

In four animals, bursts of spontaneous Parkinsonian-like tremor of 4-8 cycles/sec. could be observed. They occurred after the peak akinesia had been reached, that is between 6-8 hours after the injection. They were more obvious in monkey H-91. They lasted 12 to 14 hours. In one animal tremor was first noted on the second day of treatment.

All monkeys reacted to harmaline (3mg/kg i.m.) by showing, after 15 minutes, a reproducible Parkinsonian-like tremor of the limbs and head. It was comparable to the tremor elicited by harmaline in monkeys with a cerebellar lesion. It could be observed on the first day of haloperidol treatment and at any time during treatment. Six months after withdrawal of haloperidol, when the behavior of the animals was almost indistinguishable from normal, harmaline (3mg/kg i.m.) would still elicit the same tremor in all monkeys that had received haloperidol chronically.

**DISCUSSION**

The initial period of restlessness displayed by monkeys chronically receiving haloperidol could correspond to the akathisia observed in human patients. We could find no histological change in the brain of the monkey who showed circling during this period. Whether this ex-

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**TABLE I**

Symptoms observed during a 24-hour period following haloperidol (0.25mg/kg i.m.), 3 months after the beginning of treatment. Chewing movements in one monkey and harmaline-induced postural tremor in all six monkeys could be seen at any time. Numbers in brackets indicate the number of monkeys exhibiting the symptom.

<table>
<thead>
<tr>
<th>Time after haloperidol</th>
<th>Restlessness</th>
<th>Akathisia</th>
<th>Circling</th>
<th>Progressive Akinesia</th>
<th>Postural Tremor</th>
<th>Deep Akinesia</th>
<th>Choreoathetoid and Dystonic Movements</th>
<th>Diminishing Akinesia</th>
<th>Postural Tremor</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-½ h.</td>
<td>(6)</td>
<td></td>
<td>(1)</td>
<td>(4)</td>
<td>(6)</td>
<td>(6)</td>
<td>(1)</td>
<td>(4)</td>
<td>(6)</td>
</tr>
<tr>
<td>½-1 h.</td>
<td>(6)</td>
<td></td>
<td>(1)</td>
<td>(4)</td>
<td>(6)</td>
<td>(6)</td>
<td>(1)</td>
<td>(4)</td>
<td>(6)</td>
</tr>
<tr>
<td>1-6 h.</td>
<td>(6)</td>
<td></td>
<td>(1)</td>
<td>(4)</td>
<td>(6)</td>
<td>(6)</td>
<td>(1)</td>
<td>(4)</td>
<td>(6)</td>
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<tr>
<td>6-12 h.</td>
<td>(6)</td>
<td></td>
<td>(1)</td>
<td>(4)</td>
<td>(6)</td>
<td>(6)</td>
<td>(1)</td>
<td>(4)</td>
<td>(6)</td>
</tr>
<tr>
<td>12-24 h.</td>
<td>(6)</td>
<td></td>
<td>(1)</td>
<td>(4)</td>
<td>(6)</td>
<td>(6)</td>
<td>(1)</td>
<td>(4)</td>
<td>(6)</td>
</tr>
</tbody>
</table>

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**Figure 1**—8 mm film strip (18 frames/sec.) showing athetoid movements of the left hand in monkey H-91 two hours after his daily dose of haloperidol (0.25mg/kg i.m.), one month after the beginning of the experiment. Note successively from A to H, fanning of the fingers, hyperextension and adduction of the fingers and supination of the hand. The animal was otherwise very akinetic. The sequence shown lasts approximately 0.5 second.
citement corresponds to an agonistic effect of haloperidol or to a transitory disinhibition is not clear.

The dystonic and choreo-athetoid movements seen in monkey H-91 are clinically reminiscent of the acute dystonic symptoms seen in human patients following neuroleptic treatment (Ayd, 1961). They occurred during the peak of akinesia and usually replaced postural tremor. They were abolished by benztpine mesylate (0.5mg/kg i.m.). Similar recurrent abnormal movements have been reported in the monkey after prolonged administration of chlorpromazine (Paulson, 1973; Deneau et al., 1969). In another study, the microscopic study of the brains of monkeys with such signs revealed possible morphological alterations of the astrocytes of the white matter (Cammermeyer, 1969). We could not find any significant morphological alteration in the brains of our monkeys.

The oral dyskinesia of monkey H-94 is the only overt symptom that persisted for 6 months after cessation of haloperidol. Histological examination of the brain of this monkey revealed a normal substantia nigra and mesencephalic nuclei. Alterations of these cell groups have been reported in human patients presenting tardive dyskinesia (Christensen et al., 1970).

Akinnesia resembling Parkinsonism was seen in all monkeys following the daily injections of haloperidol. Postural tremor (3-8 cycles/sec.) was also present consistently in one monkey and occasionally in three others. Similar to our previous observations (Bédard et al., 1970; Larochelle et al., 1971), tremor is conspicuous before and after the peak of akinnesia. During the akinetic period, the limbs appeared to be more rigid as assessed by passive mobilization.

Parkinsonian-like postural tremor has been ascribed to a combined involvement of the nigrostriatal dopaminergic pathway and of the corresponding neocerebellum and related brain stem structures (parvicellular red nucleus and inferior olivary nucleus) (Poirier et al., 1966; Larochelle et al., 1970; Poirier, 1970). Blockade of dopaminergic transmission is consistent with current theories on the mode of action of haloperidol (Janssen, 1967), but the drug must also induce a functional impairment of the neocerebellum and related brain stem structures. Selective accumulation of haloperidol has been detected by autoradiography in the cerebellum and especially in the Purkinje cells (Scarlato et al., 1967). This was confirmed biochemically by Janssen et al. (1968). It should also be remembered that there are noradrenergic pathways in the cerebellum (Hokfelt et al., 1969) that could be blocked by haloperidol.

Such impairment of the cerebellum is also necessary to explain the harmaline-induced tremor which has been observed only in connection with lesions of the neocerebellum and related structures. The presence of harmaline-induced tremor 6 months after withdrawal of haloperidol shows that this impairment is long lasting if not permanent. It has not been reported in humans since, without the harmaline test, it would have been undetected in our animals.

The cerebral vascular disease found in one monkey at the histological examination is probably a coincidental finding, but ought to be kept in mind should such pathology be reported in other studies.

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REFERENCES

