RESULTS

Motor activity (Photoactometer):

Apomorphine (5mg/kg) amphetamine (5mg/kg); L-dopa (200mg/kg) and SK & F 38393 (5mg/kg) increased significantly number of counts.

Pimozide (0.5mg/kg) depressed the animal activity but when pimozide (0.5mg/kg) was given to animals prior to dopaminergic agonists, hyperactivity induced by these agents was reduced significantly.

Lolazolme, propranolol and methysergide in the doses of 2mg/kg each did not produce effect on stimulation caused by dopaminergic agents. Further, we observed in our study that reserpine (5mg/kg) did not produce any alternation in action of dopaminergic drugs. Nialamide potentiated the action of L-dopa, apomorphine, amphetamine and SKF 38393. (Table-4, Fig-9A, 9B, 9C and 9D).

Immobility in mice:

The mice when replaced in cylinder (box) 24 h after the first test showed immobility of prolonged duration. This prolonged duration of immobility was reduced by the treatment with apomorphine (5mg/kg), L-dopa (200mg/kg),
### Effect of Dopaminergic Agents on Psychomotoractivity of Mice

**Photoactometer**

<table>
<thead>
<tr>
<th>Sr.No.</th>
<th>Treatment</th>
<th>Dose (i.p.)</th>
<th>0 min.</th>
<th>Mean count (± SE) taken at</th>
<th>30 min.</th>
<th>60 min.</th>
<th>90 min.</th>
<th>120 min.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Apomorphine</td>
<td>5mg/kg</td>
<td>209.4±18.23</td>
<td>227.2±16.90</td>
<td>257.4±18.13</td>
<td>226.4±11.18</td>
<td>251.8±11.82</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>Amphetamine</td>
<td>5mg/kg</td>
<td>183.4±5.63</td>
<td>219.0±11.69</td>
<td>256.0±10.53</td>
<td>272.8±8.52</td>
<td>249.8±7.99</td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>SK &amp; F 38393</td>
<td>5mg/kg</td>
<td>193.8±8.58</td>
<td>207.8±7.97</td>
<td>190.4±8.15</td>
<td>196.60±6.08</td>
<td>193.2±4.45</td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>L-dopa</td>
<td>200mg/kg</td>
<td>170.2±13.19</td>
<td>196.8±4.80</td>
<td>225.8±7.47</td>
<td>249.2±10.19</td>
<td>220.4±6.88</td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td>Apomorphine + Pimozide</td>
<td>5mg/kg + 0.5mg/kg</td>
<td>135.0±14.79</td>
<td>135.4±16.88</td>
<td>130.4±17.15</td>
<td>127.4±19.10</td>
<td>121.0±17.13</td>
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</tr>
<tr>
<td>6.</td>
<td>Amphetamine + Pimozide</td>
<td>5mg/kg + 0.5mg/kg</td>
<td>132.0±3.85</td>
<td>130.0±3.34</td>
<td>134.0±2.40</td>
<td>129.2±3.20</td>
<td>130.0±2.17</td>
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<tr>
<td>7.</td>
<td>L-dopa + Pimozide</td>
<td>200mg/kg + 0.5mg/kg</td>
<td>228.0±7.24</td>
<td>245.3±25.93</td>
<td>235.3±23.97</td>
<td>208.6±9.62</td>
<td>197.0±17.71</td>
<td></td>
</tr>
<tr>
<td>8.</td>
<td>SK &amp; F 38393 + Pimozide</td>
<td>5mg/kg + 0.5mg/kg</td>
<td>193.8±8.58</td>
<td>190.4±8.15</td>
<td>193.2±6.08</td>
<td>193.2±0.88</td>
<td>190.0±8.15</td>
<td></td>
</tr>
<tr>
<td>9.</td>
<td>Pimozide</td>
<td>0.5mg/kg</td>
<td>196.3±3.76</td>
<td>173.0±10.01</td>
<td>149.0±8.04</td>
<td>145.0±7.81</td>
<td>168.6±1.02</td>
<td></td>
</tr>
<tr>
<td>10.</td>
<td>Nialamide + L-dopa</td>
<td>20mg/kg</td>
<td>180.4±2.92</td>
<td>160.8±2.07</td>
<td>146.4±2.07</td>
<td>145.2±2.53</td>
<td>144.6±1.91</td>
<td></td>
</tr>
<tr>
<td>11.</td>
<td>Nialamide - Apomorphine</td>
<td>20mg/kg - 5mg/kg</td>
<td>241.3±14.54</td>
<td>186.0±11.78</td>
<td>174.6±11.47</td>
<td>178.0±15.10</td>
<td>180.6±9.59</td>
<td></td>
</tr>
<tr>
<td>Sr.No.</td>
<td>Treatment</td>
<td>Dose (i.p.)</td>
<td>0 min.</td>
<td>Mean count (± SE) taken at</td>
<td></td>
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<td></td>
<td></td>
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<td>30 min.</td>
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<td>60 min.</td>
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<td>90 min.</td>
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<tr>
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<td></td>
<td>120 min.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12.</td>
<td>Nialamide + Amphetamine</td>
<td>2mg/kg</td>
<td>230.33±6.36</td>
<td>198.23±8.17</td>
<td>164.0±13.50</td>
<td>130.66±6.69</td>
<td>140.30±5.84</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5mg/kg</td>
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<td></td>
</tr>
<tr>
<td>13.</td>
<td>Nialamide + L-dopa</td>
<td>20mg/kg</td>
<td>186.4±2.92</td>
<td>143.8±2.31</td>
<td>127.8±1.97</td>
<td>147.6±6.48</td>
<td>117.4±20.24</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>5mg/kg</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>14.</td>
<td>Nialamide + SK &amp; F 38393</td>
<td>20mg/kg</td>
<td>222.33±8.77</td>
<td>313.00±11.51</td>
<td>322.00±20.62</td>
<td>284.60±21.50</td>
<td>235.00±14.12</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5mg/kg</td>
<td></td>
<td></td>
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<tr>
<td>15.</td>
<td>Reserpine + Apomorphine</td>
<td>5mg/kg</td>
<td>66.66±8.09</td>
<td>56.0±5.53</td>
<td>57.0±7.23</td>
<td>53.3±5.91</td>
<td>50.3±5.91</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5mg/kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>16.</td>
<td>Reserpine + Amphetamine</td>
<td>5mg/kg</td>
<td>77.33±2.96</td>
<td>73.0±3.80</td>
<td>70.3±6.01</td>
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<tr>
<td></td>
<td></td>
<td>5mg/kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17.</td>
<td>Reserpine</td>
<td>5mg/kg</td>
<td>53.0±7.77</td>
<td>53.86±7.52</td>
<td>52.33±9.36</td>
<td>54.66±8.11</td>
<td>54.66±8.66</td>
<td></td>
</tr>
<tr>
<td>18.</td>
<td>Reserpine + L-dopa</td>
<td>5mg/kg</td>
<td>76.40±1.52</td>
<td>61.3±1.75</td>
<td>54.66±8.11</td>
<td>48.1±1.09</td>
<td>45.5±1.51</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>200mg/kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19.</td>
<td>Reserpine + SK &amp; F 38393</td>
<td>5mg/kg</td>
<td>78.40±2.64</td>
<td>71.1±1.91</td>
<td>70.3±6.01</td>
<td>76.33±2.02</td>
<td>76.2±0.93</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5mg/kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Figure 9: Motor activity studied with Photoactometer

The figures show the cumulative counts of motor activity of a group of five mice, tested in the photoactometer (Techno).

(A) Apomorphine-5mg/kg, Amphetamine-5mg/kg, SK & F 38393-5mg/kg and L-dopa-200mg/kg.

Note the significant increase in the numbers of counts.

(B) Pimozide at the dose of 0.5mg/kg decreases the hyper activity induced by apomorphine (5mg/kg), amphetamine (5mg/kg) and L-dopa (200mg/kg).

(C) Nialamide (5mg/kg) potentiated the action of L-dopa, Apomorphine and Amphetamine.

(D) Reserpine (5mg/kg) failed to produce any alteration in the action of dopaminergic drugs i.e. Apomorphine and Amphetamine.

Ordinate: Cumulative counts over five minutes.
Abscissa: Time in minutes after I.P. injection.
SK & F 38393 (5mg/kg), amphetamine (5mg/kg) and imipramine (20mg/kg). (Fig. 10A). On the other hand in our study we have noted that pimozide (0.5mg/kg), haloperidol (4.0mg/kg), and metoclopramide (5mg/kg), the dopamine receptor blocking agents enhanced the prolongation of immobility. Same type of enhancement was also observed with depletator of catecholamine, reserpine (2mg/kg). (Fig. 10B).

**Muscle exhaustion test (Swimming to Exhaustion):**

Test animals (mice) were put on the wheel when wheel was rotated over the water bath, in the way so that mice completely immerse in the water level. Parameter to be noted, being the number of rotations or time period which mice withstand the water immersion, while on wheel.

In the present study dopaminergic agonists reduced the muscular strength, significantly (P<0.001). The dopaminergic receptor blocking agent, pimozide failed to produce any action, but antagonised the action of dopaminergic drugs. There was no change in muscular strength of reserpinised mice (Table-5).

**Stereotype behaviour:**

In present study, number of rats receiving each treatment was 15. Rats receiving, apomorphine, L-dopa or amphetamine showed stereotype behaviour of score 3. However, when rats were treated with SK & F 38393 5mg/kg they failed to show the stereotype behaviour.
IMMOBILITY IN MICE

Fig. 10

A

DURATIONS OF IMMOBILITY (S)

Control Apomorphine L-Dopa SK&F 38393 Amphetamine
5 mg/kg 200 mg/kg 5 mg/kg 5 mg/kg

B

DURATION OF IMMOBILITY (S)

Control Pimozide Haloperidol Reserpine Metoclopramide
(0.5) (4.0) (5) (5)

(mg/kg IP)
Table - 5

**SWIMMING TEST (Muscle Exhaustion Test)**

<table>
<thead>
<tr>
<th>Sr.No.</th>
<th>Treatment</th>
<th>Dose (i.p.) (mg/kg)</th>
<th>Mean time in (min) ± SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Saline (Control)</td>
<td>-</td>
<td>10.16 ± 0.26</td>
</tr>
<tr>
<td>2</td>
<td>L-dopa</td>
<td>200mg/kg</td>
<td>5.07 ± 0.53**</td>
</tr>
<tr>
<td>3</td>
<td>Apomorphine</td>
<td>5mg/kg</td>
<td>5.13 ± 0.52*</td>
</tr>
<tr>
<td>4</td>
<td>SK &amp; F 38393</td>
<td>5mg/kg</td>
<td>5.33 ± 0.40*</td>
</tr>
<tr>
<td>5</td>
<td>Amphetamine</td>
<td>5mg/kg</td>
<td>5.14 ± 0.30*</td>
</tr>
<tr>
<td>6</td>
<td>Reserpine</td>
<td>5mg/kg (3 days)</td>
<td>9.55 ± 0.30</td>
</tr>
<tr>
<td>7</td>
<td>Pimozide</td>
<td>0.5mg/kg</td>
<td>9.25 ± 10.54</td>
</tr>
<tr>
<td>8</td>
<td>Pimozide + apomorphine</td>
<td>0.5mg/kg + 5mg/kg</td>
<td>9.55 ± 0.30</td>
</tr>
<tr>
<td>9</td>
<td>Pimozide + Amphetamine</td>
<td>0.5mg/kg + 5mg/kg</td>
<td>9.25 ± 0.54</td>
</tr>
<tr>
<td>10</td>
<td>Pimozide + SK &amp; F 38393</td>
<td>0.5mg/kg + 5mg/kg</td>
<td>8.25 ± 0.30</td>
</tr>
<tr>
<td>11</td>
<td>Pimozide + L-dopa</td>
<td>0.5mg/kg + 200mg/kg</td>
<td>9.20 ± 0.52</td>
</tr>
</tbody>
</table>

**P Value:**

* Significantly different from control $P < 0.01$

** Significantly different from control $P < 0.001$

$n = 5$
Furthermore in study we observed that pimozide 0.5mg/kg did not show any stereotype behaviour (score U). When the animals were pretreated with pimozide, the stereotype actions of amphetamine, L-dopa or apomorphine was antagonised (score in presence of pimozide was U). However it remained unaffected when animals were pretreated with tolazoline (4mg/kg), propranolol (4mg/kg), cyproheptadine (4mg/kg), methysergide (2mg/kg) clonidine (100μg/kg), or cimetidine (2mg/mg).

Haloperidol, chlorpromazine, and metoclopramide also antagonized the stereotype induced by dopamine agonists whereas in presence of clonidine, propranolol, cyproheptadine cimetidine and methysergide-treatment failed to change the score of DA agonists.

Hebb-William-maze:
Dopaminergic drugs which were studied did not show any effect on learning behaviour.

Obstruction box:
Dopaminergic agents which were studied did not show any change in time interval after passage of current.
3. **Study related to yawning behaviour in rats:**

The results of present study indicate that L-dopa in doses of 50, 100, 150 and 200mg/kg, amphetamine in doses of 1, 2, 5 and 10mg/kg and apomorphine in doses of 0.01, 0.02, 0.05, and 0.1mg/kg produced dose dependent increase in yawning up to the period 40 minutes, whereas, SK & F 38393, a novel dopamine agonist failed to elicit this response. In case of apomorphine peak effect was observed at 0.05mg/kg. Higher doses did not further increase yawning (see fig 11A). In the dose 0.02mg/kg apomorphine caused increased locomotion and sniffing, apart from this no other behaviour was induced. The effect of apomorphine 0.05mg/kg reached peak within 15 min, remained high upto 25 min. and then declined. No yawning was observed after 40 min. L-dopa also produced dose dependent effect (Fig.11B) identical to apomorphine with peak effect observed at 150mg/kg. Amphetamine produced yawning in a much lower extent. L-dopa induced significantly (P<0.05) more yawning at 50 and 150mg/kg as compared to amphetamine. No other behavioural change was observed.

**Effect of pimozide on apomorphine, amphetamine and L-dopa induced yawning:**

Pimozide injected 30 min before apomorphine 0.05mg/kg dose dependently reduced the number of yawns (Fig.11D). There was no change in gross behaviour. Pimozide (0.5mg/kg) also blocked yawning induced by 150mg/kg L-dopa and 5mg/kg amphetamine.
**Fig. 11**

**A**

YAWNS / 40 min.  
(n=5)

**B**

YAWNS / 40 min.

**C**

n = 5

Dose of Apomorphine  
(mg/kg)  
Dose of L-Dopa  
(mg/kg)  
Dose of Amphetamine  
(mg/kg)

**D**

YAWNS / 40 min.

APO  
APO 0.05  
APO  
L-DOPR  
L-DOPR  
L-DOPR  
AMT  
AMT  
AMT  
+  
+  
+  
+  
Pimozide  
0.05 mg/kg  
Pimozide  
0.5 mg/kg  
Domperidone  
2 mg/kg  
DMP  
0.5 mg/kg

**Fig. 11**
Effect of domperidone:

Domperidone injected 30 min. before apomorphine 0.05mg/kg did not antagonise the yawning responses. However, the highest dose (3mg/kg) enhanced the yawning induced by apomorphine.

Role of dopaminergic mechanism in aggressive behaviour:

Apomorphine elicited stereotype gnawing and licking in normal rats and fighting response in reserpine-treated rats. The fighting response was characterised by bouts of fighting between rats in anatomical proximity. The wrestling bouts consisted of striking with their forelegs while standing on their hindlegs. Intense vocalisation and biting accompanied the attacks. The fighting was fierce after 30 min. and completely disappeared after 2h. Sex did not make any difference in the fighting response.

Maximum fighting scores were obtained when apomorphine (125mg/kg) was administered to rats 4h after reserpine administration.

Chlorpromazine, haloperidol, pimozide, and metoclopramide an hour before the administration of apomorphine blocked the usual fighting response to reserpine-apomorphine combination (Table 6).

L-dopa, SK & F 38393 and amphetamine administered an 30 min. before the administration of apomorphine, elicited the fighting response (see table) whereas same response was not when animals were treated with nialamide.
Table 6
Role of dopaminergic mechanism in aggressive behaviour

<table>
<thead>
<tr>
<th>Pre-treatment</th>
<th>Challenging Agent</th>
<th>Fighting Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reserpine (5mg/kg)</td>
<td>Apomorphine (1.25mg/kg)</td>
<td>410</td>
</tr>
<tr>
<td></td>
<td>Chlorpromazine (5mg/kg)</td>
<td></td>
</tr>
<tr>
<td>4 hr before</td>
<td>Apomorphine (1.25mg/kg)</td>
<td></td>
</tr>
<tr>
<td>Reserpine (5mg/kg)</td>
<td>Haloperidol (4mg/kg)</td>
<td>0</td>
</tr>
<tr>
<td>4 hr before</td>
<td>Apomorphine (1.25mg/kg)</td>
<td></td>
</tr>
<tr>
<td>Reserpine (5mg/kg)</td>
<td>Pimozide (0.5mg/kg)</td>
<td>0</td>
</tr>
<tr>
<td>4 hr before</td>
<td>Apomorphine (1.25mg/kg)</td>
<td></td>
</tr>
<tr>
<td>Reserpine (5mg/kg)</td>
<td>Metoclopramide (5mg/kg)</td>
<td>0</td>
</tr>
<tr>
<td>4 hr before</td>
<td>Apomorphine (1.25mg/kg)</td>
<td></td>
</tr>
<tr>
<td>Reserpine (5mg/kg)</td>
<td>L-dopa (200mg/kg)</td>
<td>525</td>
</tr>
<tr>
<td>4 hr before</td>
<td>Apomorphine (1.25mg/kg)</td>
<td></td>
</tr>
<tr>
<td>Reserpine (5mg/kg)</td>
<td>Amphetamine (5mg/kg)</td>
<td>610</td>
</tr>
<tr>
<td>4 hr before</td>
<td>Apomorphine (1.25mg/kg)</td>
<td></td>
</tr>
<tr>
<td>Reserpine (5mg/kg)</td>
<td>SK &amp; F 38393 (5mg/kg)</td>
<td>415</td>
</tr>
<tr>
<td>40 min before</td>
<td>Apomorphine (1.25mg/kg)</td>
<td></td>
</tr>
<tr>
<td>Imipramine (20mg/kg)</td>
<td>Reserpine (5mg/kg)</td>
<td>0</td>
</tr>
<tr>
<td>3 days before</td>
<td>Apomorphine (1.25mg/kg)</td>
<td></td>
</tr>
<tr>
<td>Reserpine (5mg/kg)</td>
<td>Imipramine (20mg/kg)</td>
<td>350</td>
</tr>
<tr>
<td>3 days treatment</td>
<td>Apomorphine (1.25mg/kg)</td>
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</tr>
<tr>
<td>Reserpine (5mg/kg)</td>
<td>Nialamide (2mg/kg)</td>
<td>675</td>
</tr>
<tr>
<td>4 hr before</td>
<td>Apomorphine (1.25mg/kg)</td>
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<td>Pre-treatment</td>
<td>Challenging Agent</td>
<td>Fighting Scores</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Reserpine (5mg/kg)</td>
<td>Cyproheptadine (4mg/kg)</td>
<td>Apomorphine (1.25mg/kg)</td>
</tr>
<tr>
<td>4 hr before</td>
<td>1 hr before</td>
<td></td>
</tr>
<tr>
<td>Reserpine (5mg/kg)</td>
<td>Tolazoline (2mg/kg)</td>
<td>Apomorphine (1.25mg/kg)</td>
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</tr>
<tr>
<td>Reserpine (5mg/kg)</td>
<td>Mepyramine (2mg/kg)</td>
<td>Apomorphine (1.25mg/kg)</td>
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<tr>
<td>4 hr before</td>
<td>1 hr before</td>
<td></td>
</tr>
<tr>
<td>Reserpine (5mg/kg)</td>
<td>Cimetidine (4mg/kg)</td>
<td>Apomorphine (1.25mg/kg)</td>
</tr>
<tr>
<td>4 hr before</td>
<td>1 hr before</td>
<td></td>
</tr>
</tbody>
</table>
When imipramine (20mg/kg) was given for 3 days followed by reserpine given 4 hr before the apomorphine challenge, the fighting response was blocked. However, when reserpine was given for 3 days followed by imipramine given 4 hr before the apomorphine challenge, there was fighting tendency induced in animals.

**Effect of different dopamine antagonists on isolation syndrome in mice:**

For producing the isolation syndrome the procedure described by Valzelli et al., (1967) was followed. The aggressive behaviour developed after a period of six weeks. On the day of experiment the two isolated mice were brought together and the exchanges between them were scored as described by Valzelli et al. (1967). The observation period was for 5 minutes. The results are tabulated in (Table 7).

The results indicate the effectiveness of dopamine antagonists in inhibiting post isolation syndrome. Further isolation syndrome is reflexation of psychoneurosis in human beings.
Table - 7

Effects of different dopamine antagonists on score in post-isolation paired mice:

<table>
<thead>
<tr>
<th>Sr.No.</th>
<th>Pretreatment</th>
<th>Average Score Before (control)</th>
<th>SE</th>
<th>Average Score After (Treated)</th>
<th>SE</th>
<th>P &lt;</th>
<th>% Inhibition in treated mice</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pimozide</td>
<td>100</td>
<td>0.10</td>
<td>15</td>
<td>10.0</td>
<td>0.001</td>
<td>85.0</td>
</tr>
<tr>
<td>2</td>
<td>Haloperidol</td>
<td>90</td>
<td>6.12</td>
<td>15</td>
<td>10.0</td>
<td>0.001</td>
<td>83.3</td>
</tr>
<tr>
<td>3</td>
<td>Metoclopra-</td>
<td>95</td>
<td>6.12</td>
<td>35</td>
<td>18.70</td>
<td>0.05</td>
<td>58.8</td>
</tr>
<tr>
<td></td>
<td>mide</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Cyproheptadine</td>
<td>85</td>
<td>6.12</td>
<td>79</td>
<td>1.06 N.S.</td>
<td>7.05</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Saline</td>
<td>100</td>
<td>0.00</td>
<td>100</td>
<td>0.00</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

n = 10
Effects of apomorphine, SK & F 38393 and L-dopa on haloperidol induced catalepsy:

Dopamine agonists antagonized, haloperidol induced catalepsy to variable extent (Table 8). Apomorphine produced dose-dependent antagonism of haloperidol induced catalepsy whereas, L-dopa in different doses produced identical increase in latency period, SK & F 38393 produced marked antagonism of haloperidol induced catalepsy at 5mg/kg. However in the presence of 10mg/kg SK & F 38393 haloperidol failed to produce any catalepsy, similarly amphetamine completely antagonized the cataleptic response.

Effect on sleeping time:

Prostaglandin E₁ (PGE₁) (50ng/kg and 100ng/kg, i.p.) produced significant potentiation (P < 0.001) of pentobarbitone induced sleeping time in mice (Table 9,10), rats (Table 11) and chicks (Table 12). Animal receiving PGE₁ before pentobarbitone sodium (100mg/kg) became quiescent, huddled together in the corner and closed the palpebral fissure. The sedative effect was evident within 10-15 minutes.

The interaction of PGE₁ on pentobarbitone sleeping time was studied with agents blocking α-adrenoceptors (tolazoline), β-adrenoceptors (pronethalol), serotonin (cyproheptadine) and dopamine receptors (Pimozide, haloperidol and metoclopramide). It was found that all dopamine receptor
### Table 8

**Effect of Apomorphine, SK & F 38393 and L-dopa on Haloperidol induced catalepsy:**

<table>
<thead>
<tr>
<th>Treatment in mg/kg, i.p.</th>
<th>No. of animal</th>
<th>Mean cataleptic score at different interval in minutes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>20</td>
</tr>
<tr>
<td>1. 0.5 Halo-peridol</td>
<td>16</td>
<td>3.00</td>
</tr>
<tr>
<td>2. 5.0 + 0.5 (Apo.+Halo)</td>
<td>8</td>
<td>2.75±0.21</td>
</tr>
<tr>
<td>3. 10.0 + 0.5 (Apo.+Halo)</td>
<td>5</td>
<td>2.12±0.29</td>
</tr>
<tr>
<td>4. 5.0 + 0.5 (SK &amp; F 38393 + Halo)</td>
<td>5</td>
<td>1.60±0.21</td>
</tr>
<tr>
<td>5. 10.0 + 0.5 (SK &amp; F 38393 + Haloperidol)</td>
<td>5</td>
<td>No catalepsy</td>
</tr>
<tr>
<td>6. 100.00 + 0.5 (L-dopa + Haloperidol)</td>
<td>5</td>
<td>2.54±0.26</td>
</tr>
<tr>
<td>7. 200.00 + 0.5 (L-dopa + Haloperidol)</td>
<td>5</td>
<td>2.50±0.25</td>
</tr>
<tr>
<td>8. 5.0 + 0.5 (Apo.+Halo)</td>
<td>5</td>
<td>No catalepsy</td>
</tr>
</tbody>
</table>

**Remarks:**

Results are expressed in mean ± SEM.

In each case animals were observed for period of 120 minutes for the development of cataleptic state.

* P < 0.01 and ** P < 0.001 vs. haloperidol

*** P < 0.001 vs. haloperidol
blockers prevented PGE\(_1\) induced potentiation of pentobarbitone sleeping time in rats (Table 11), mice (Table 9, 10) and chicks (Table 12). Even the normal pentobarbitone sleeping time was significantly (P < 0.001) reduced by pimozide in all the three species studied. Haloperidol also reduced the pentobarbitone sleeping time but it was significant in chicks only.

Unlike that of dopaminergic blockers, tolazoline pronethalol or cyproheptadine failed to prevent PGE\(_1\) induced potentiation of pentobarbitone sleeping time (Table 10, 11, 12).

"Sleep Index" was calculated by multiplying the average sleeping time of group with the percent sleeping animals in that group.

Sleeping time:

Dopaminergic blocking drugs significantly reduced the sleep induced by ethanol (Table 13) whereas, dopamine agonists caused the potentiation of ethanol sleeping time (Table 13).
**Table 9**

**Effect of different antagonists on the duration of sleep induced by pentobarbitone and PGE₁ in mice**

Dose of Pentobarbitone: 100mg/kg i.p.  
Dose of PGE₁: 50mg/kg i.p.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (I.P.)</th>
<th>No. of Animals</th>
<th>% animals slept</th>
<th>Mean duration of sleep (minutes±SE)</th>
<th>Sleep Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline + Pentobarbitone</td>
<td>-</td>
<td>8</td>
<td>100</td>
<td>159.77 ± 3.76</td>
<td>15977</td>
</tr>
<tr>
<td>PGE₁ + Pentobarbitone</td>
<td>-</td>
<td>8</td>
<td>100</td>
<td>254.15 ± 7.10xxx</td>
<td>25415</td>
</tr>
<tr>
<td>PGE₁ + Pentobarbitone + Tolazoline + Pronethalol</td>
<td>4mg/kg</td>
<td>5</td>
<td>100</td>
<td>238.00 ± 16.79</td>
<td>23800 NS</td>
</tr>
<tr>
<td>PGE₁ + Pentobarbitone + Haloperidol</td>
<td>4mg/kg</td>
<td>8</td>
<td>100</td>
<td>143.60 ± 3.35xxx</td>
<td>14360</td>
</tr>
<tr>
<td>PGE₁ + Pentobarbitone + Pimozide</td>
<td>0.5mg/kg</td>
<td>10</td>
<td>100</td>
<td>130.48 ± 4.34xxx</td>
<td>13048</td>
</tr>
<tr>
<td>PGE₁ + Pentobarbitone + Metaclopramide</td>
<td>5mg/kg</td>
<td>10</td>
<td>80</td>
<td>139.72 ± 3.01xx</td>
<td>13972</td>
</tr>
</tbody>
</table>

\[ xx = P < 0.01 \]
\[ xxx = P < 0.001 \]
Table 10

Effect of different antagonists on the duration of sleep induced by pentobarbitone sodium and PGE₁ in mice:

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Dose (I.P.)</th>
<th>No. of Animals</th>
<th>% of animal slept</th>
<th>Mean duration of sleep (minutes ± SE)</th>
<th>Sleep Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline + Pentobarbitone</td>
<td></td>
<td>10</td>
<td>100</td>
<td>87.13 ± 4.41</td>
<td>8713</td>
</tr>
<tr>
<td>PGE₁ + Pentobarbitone</td>
<td></td>
<td>6</td>
<td>100</td>
<td>163.15 ± 6.87**</td>
<td>16315</td>
</tr>
<tr>
<td>PGE₁ + Pimozide + Pentobarbitone</td>
<td>0.5mg/kg</td>
<td>6</td>
<td>100</td>
<td>133.14 ± 4.0*</td>
<td>13311</td>
</tr>
<tr>
<td>PGE₁ + Pentobarbitone + Haloperidol</td>
<td>4mg/kg</td>
<td>10</td>
<td>100</td>
<td>139.72 ± 2.92*</td>
<td>13972</td>
</tr>
<tr>
<td>PGE₁ + Pentobarbitone + Priscol + Pronethamol</td>
<td>5mg/kg + 2mg/kg</td>
<td>6</td>
<td>100</td>
<td>154.61 ± 8.12</td>
<td>15461</td>
</tr>
<tr>
<td>PGE₁ + Pentobarbitone + Cyproheptadine</td>
<td>4mg/kg</td>
<td>6</td>
<td>100</td>
<td>167.50 ± 3.10</td>
<td>16750</td>
</tr>
</tbody>
</table>

* P < 0.01
** P < 0.001
Table - 11

Effect of different antagonist on the duration of sleep induced by pentobarbitone sodium and PGE₁ in rats:

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Dose (I.P.)</th>
<th>No. of Animals</th>
<th>% of Animals slept</th>
<th>Mean duration of sleep (Minutes ± SE)</th>
<th>Sleep Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline + Pentobarbitone</td>
<td>-</td>
<td>5</td>
<td>100</td>
<td>104 ± 7.85</td>
<td>10400</td>
</tr>
<tr>
<td>PGE₁ + Pentobarbitone</td>
<td>-</td>
<td>5</td>
<td>100</td>
<td>163.57 ± 20.34*</td>
<td>16357</td>
</tr>
<tr>
<td>PGE₁ + Pentobarbitone + Haloperidol</td>
<td>4mg/kg</td>
<td>5</td>
<td>100</td>
<td>109.00 ± 5.80**</td>
<td>10900</td>
</tr>
<tr>
<td>PGE₁ + Pentobarbitone + Pimozide</td>
<td>0.5mg/kg</td>
<td>5</td>
<td>100</td>
<td>66.17 ± 3.42***</td>
<td>6617</td>
</tr>
<tr>
<td>PGE₁ + Pentobarbitone + Cyprohepatedine</td>
<td>4mg/kg</td>
<td>5</td>
<td>100</td>
<td>159.00 ± 10.35*</td>
<td>15900</td>
</tr>
<tr>
<td>PGE₁ + Pentobarbitone + Priscol + Pronethalol (tolazoline)</td>
<td>5mg/kg</td>
<td>5</td>
<td>100</td>
<td>159.00 ± 15.14*</td>
<td>15900</td>
</tr>
</tbody>
</table>

Dose of Pentobarbitone sodium : 100mg/kg
Dose of PGE₁*: 100ng/kg

P < 0.05
** P < 0.01
*** P < 0.001
**Table - 12**

**Effect of different antagonists on the duration of sleep induced by Pentobarbitone sodium and PGE₁ in chicks:**

Dose of Pentobarbitone sodium: 100mg/kg  
Dose of PGE₁: 100ng/kg

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Dose (I.P.)</th>
<th>No. of Animals</th>
<th>% of animals slept</th>
<th>Mean duration of slept (Minutes ± SE)</th>
<th>Sleep Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline + Pentobarbitone</td>
<td>-</td>
<td>4</td>
<td>100</td>
<td>140 ± 2.3</td>
<td>14000</td>
</tr>
<tr>
<td>PGE₁ + Pentobarbitone</td>
<td>-</td>
<td>4</td>
<td>100</td>
<td>190 ± 2.18*</td>
<td>19000</td>
</tr>
<tr>
<td>PGE₁ + Pentobarbitone + Haloperidol</td>
<td>4mg/kg</td>
<td>4</td>
<td>100</td>
<td>66.17 ± 3.42*</td>
<td>6617</td>
</tr>
<tr>
<td>PGE₁ + Pentobarbitone + Pimozide</td>
<td>0.5mg/kg</td>
<td>4</td>
<td>100</td>
<td>64.00 ± 2.89</td>
<td>6400</td>
</tr>
<tr>
<td>PGE₁ + Pentobarbitone + Cyproheptadine</td>
<td>4mg/kg</td>
<td>4</td>
<td>100</td>
<td>148.97 ± 1.69</td>
<td>14897</td>
</tr>
<tr>
<td>PGE₁ + Pentobarbitone + Priscol + Pronethalol</td>
<td>5mg/kg</td>
<td>5</td>
<td>100</td>
<td>163.57 ± 20.54</td>
<td>16357</td>
</tr>
</tbody>
</table>

* P < 0.001
### Table 13

Effect of dopamine antagonist and agonists on the duration of sleep due to ethanol in mice:

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Dose (mg/kg, i.p.)</th>
<th>Mean duration of sleep (minutes ± SE of the mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline (control)</td>
<td>-</td>
<td>37 ± 0.47</td>
</tr>
<tr>
<td>Pimozide</td>
<td>0.5 mg/kg</td>
<td>15 ± 1.24*</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>4 mg/kg</td>
<td>19 ± 1.56*</td>
</tr>
<tr>
<td>Melocploramide</td>
<td>5 mg/kg</td>
<td>21 ± 1.57*</td>
</tr>
<tr>
<td>Domperidone</td>
<td>5 mg/kg</td>
<td>24 ± 1.52*</td>
</tr>
<tr>
<td>Propranolol</td>
<td>2 mg/kg</td>
<td>32 ± 1.52</td>
</tr>
<tr>
<td>Cyproheptadine</td>
<td>4 mg/kg</td>
<td><em>32 ± 2.90</em></td>
</tr>
<tr>
<td>Cimetidine + Mepyramine</td>
<td>2 mg/kg</td>
<td>36 ± 2.20</td>
</tr>
<tr>
<td>L-dopa</td>
<td>200 mg/kg</td>
<td>65.63 ± 1.80*</td>
</tr>
<tr>
<td>Apomorphine</td>
<td>5 mg/kg</td>
<td>44.9 ± 2.52*</td>
</tr>
<tr>
<td>SK &amp; F 38393</td>
<td>5 mg/kg</td>
<td>32 ± 1.11</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>5 mg/kg</td>
<td>36 ± 2.25</td>
</tr>
</tbody>
</table>

* Value significantly (P < .05) different from value obtained from control.

**xx Time between loss and return of righting reflex 3.6 gm/kg i.p. diluted in saline volume of injection 0.8 ml/mouse.
Effect on body temperature:

The rectal temperature in rats was found to be quite stable during experimental period of over 120 mins. The mean rectal temperature was 37.65°C.

Dopamine (5 and 10µg/rat icv) produced a time dependent fall in body temperature. The maximum hypothermic effect was observed at the end of 30 minutes. It partially recovered towards the normal body temperature after 60 minutes and 120 minutes. Moreover at 120 minutes the body temperature was significantly lowered as compared to control.

Apomorphine (2.5 to 10mg/kg i.p.) produced time dependent fall in rectal temperature. The maximum fall was observed at the end of 30 minutes, apomorphine was found to be more potent as compared to dopamine. The maximum fall with apomorphine was 1.4 ± 0.17°C whereas that with dopamine was 0.87 ± 0.12°C (Fig.12A). Further, the fall in rectal temperature with apomorphine was dose dependent.

Like dopamine and apomorphine, L-dopa also produced time dependent fall in rectal temperature. However, the fall in temperature continued till the observation period of 120 minutes and the fall was dose dependent (Fig.12B,12C).
Figure 12: THE EFFECT OF DOPAMINERGIC AGONISTS ON THE RECTAL TEMPERATURE OF RATS:

(A) Mean changes in rectal temperature following i.c.v. injection of dopamine (5μg and 10μg/rat). At 15 and 30 minutes the results show statistically significant difference from that of the saline injected controls (n=8, P<0.05).

Room Temp. 38.5°C ± 0.21°C
Control mean body temp. = 36.92 ± 0.14°C

(B) Mean changes in rectal temperature following i.p. injection of apomorphine. Note the time dependent fall produced in rectal temperature. The maximum fall was observed at 30 minutes (n = 8).

Room Temp. 42.1°C
Control mean body temp. 37.15 ± 0.12°C

(C) Mean changes in rectal temperature following i.p. injection of L-dopa and amphetamine.

Note the time dependent fall in temperature continued till the observation period of 120 minutes. Amphetamine shows hyperthermia.

Room temp. 42.1°C
Control mean body temp. 37.56 ± 0.53°C

(D) Mean changes in rectal temperature following injection of SK & F 38393.

Note the time dependent fall produced in rectal temperature.

Room temp. 39.0°C. Control body temp. 36.92 ± 0.15°C

Each point in A, B, C and D (n=8), denotes mean and the bars are or ± SE.
Fig. 12

TIME IN MINUTES

CHANGE IN RECTAL TEMPERATURE (°C)
*SK & F 38393 also produced fall in rectal temperature, this fall was more pronounced with the dose of 5 and 10mg/kg, the maximum fall was observed at the end of 15 minutes with 10mg/kg and at the end of 30 minutes with 5mg/kg (Fig.12D).

Pimozid in the dose of 0.5mg/kg abolished completely the hypothermic effect produced by dopamine (Fig.13A), and L-dopa (Fig.13C). The responses to apomorphine and SK & F 38393 were also inhibited significantly by pimozide (Fig. 13B,13D).

Haloperidol also decreased significantly the hypothermic effect of dopamine (5ug/rat i.c.v.) and apomorphine (5mg/kg). However, haloperidol failed to antagonise the hypothermic effect of higher doses of dopamine (10ug/rat i.c.v.). Instead it potentiated the fall in body temperature produced by dopamine at the end of 120 minutes.

Studies with agents affecting brain catecholamines:

Nialamide administered to rats 1 hour prior to the injection of apomorphine (5mg/kg, i.p.) and SK & F 38393 (5mg/kg i.p.), potentiated the apomorphine and SK & F 38393 induced hypothermia (Fig.14A,14B,14C,14D). In a similar manner action of L-dopa 200mg/kg was potentiated by nialamide pretreatment. (Fig.14A,14E). Reserpine treated rats showed
Figure 13: HISTOGRAMS SHOWING MEAN CHANGES IN RECTAL TEMPERATURE OF RATS BY DOPAMINERGIC AGONISTS (DOPAMINE, APOMORPHINE, L-DOPA AND SK & F 38393) GIVEN ALONE AND AFTER PRETREATMENT WITH PIMOZIDE INJECTION i.P. 30 MINUTES BEFORE THE AGONISTS:

(A) Mean changes in rectal temperature of conscious rats following i.c.v. injection of dopamine (5 µg/rat).
Note dopamine induced hypothermia decreased by pimozide.
Room temp. 39.00°C
Mean body temp. control 37.67 ± 0.07°C.

(B) Note apomorphine induced hypothermia decreased by pimozide.
APO = Apomorphine.
Room temp. 40°C
Mean body temp. control 37.56 ± 0.13°C.

(C) Note L-dopa induced hypothermia is decreased by pimozide (0.5 mg/kg i.p.)
Room temp. 38.2°C
Mean body temp. control 37.96 ± 0.13°C

(D) Note SK & F 38393 induced hypothermia decreased by pimozide.
Room temp. 38.2°C
Mean body temp. Control 37.44 ± 0.13°C

In each group A, B, C and D (n=8)
Bars at each point show ± S.E.
All results are statistically significant (P < 0.05)
Figure 14: POTENTIATING EFFECT OF NIALAMIDE ON HYPOTHERMIA INDUCED IN RATS BY SK & F 38393, L-DOPA AND APOMORPHINE INJECTED INTRAPERITONIALLY.

(Nialamide 100 mg/kg i.p. injection 30 min. before the drugs)

Records present mean ± SE of changes in rectal temp.

(A) Note the dopaminergic agonists (SK & F 38393 and L-dopa) induced hypothermia potentiated by nialamide.

(B) Note apomorphine and SK & F 38393 induced hypothermia potentiated by nialamide.

(C) Note apomorphine induced hypothermia potentiated by nialamide.

(D) Note SK & F 38393 induced hypothermia potentiated by nialamide.

(E) Note L-dopa induced hypothermia is potentiated by nialamide.

In each group A, B, C, D & E (n=8), bars at each point show ± SE. All results are statistically significant P < 0.05 at all levels.

Room temp. 38.2°C
Mean body temp. control 37.66 ± 0.19°C
Fig. 14

A

- - CONTROL
•- • NIALAMIDE
△ - SK & F 38393 5mg/ kg + NIALAMIDE
O- • L-DOPA + NIALAMIDE

CHANGE IN RECTAL TEMPERATURE

TIME IN MINUTES

0 15 30 45 60 90 105 120

B

- - CONTROL
•- • APOMORPHINE 5mg/ kg + NIALAMIDE
△ - SK & F 38393 5mg/ kg + NIALAMIDE
O- • NIALAMIDE

CHANGE IN RECTAL TEMPERATURE

TIME IN MINUTES

0 15 30 45 60 90 105 120

C

- - CONTROL
•- • APOMORPHINE 5mg/ kg
△ - NIALAMINE
△ - APOMORPHINE 5mg/ kg + NIALAMINE

CHANGE IN RECTAL TEMPERATURE

TIME IN MINUTES

0 15 30 45 60 90 105 120

D

- - CONTROL
△ - SK & F 38393 5mg/ kg
O- • NIALAMIDE
△ - SK & F 38393 5mg/ kg + NIALAMIDE

TIME IN MINUTES

0 15 30 45 60 75 90 105 120

E

- - CONTROL
•- • L-DOPA 200mg/ kg
△ - NIALAMIDE
△ - L-DOPA 200mg/ kg + NIALAMIDE

TIME IN MINUTES

0 15 30 45 60 75 90 105 120
significant hyperthermic response as compared to control rats (P < 0.05). Apomorphine (5mg/kg, i.p.) failed to elicit its original hypothermic response in reserpiniized rats. Cocaine produced hyperthermia in rats. These animals when challenged with apomorphine (5mg/kg, i.p.) or SK & F 38393 (5mg/kg, i.p.) exhibited hypothermia.

**Anti-pyretic activity:**

I.A.B. vaccine (Table 14) produced a moderate pyrexia in all animals. The mean rise in rectal temperature at one two and three hours was 0.78°C, 1.01°C and 0.39°C respectively. Two hours was therefore decided as the cut-off time for study at anti-pyretic action of drugs.

L-dopa, apomorphine, amphetamine and SK & F 38393 in the doses mentioned in the Table 14 produced significant antipyretic effect. Whereas, pimozide had no significant antipyretic effect. It was however, observed that anti-pyretic effect of dopaminergic agonist is less pronounced.

**Food intake:**

SK & F 38393 (1mg/kg and 5mg/kg, i.p.) reduced the food intake significantly (P<0.01 and P<0.001 respectively) in rats in a dose-dependent manner (Table-16). Significant reductions in body weights were also observed. The mean increase in the body weights of 10.26 ± 1.6 in control animals
Table - 14

Anti-pyretic effects of dopaminergic agonists against TAB vaccine induced pyrexia in rats:

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Dose (mg/kg, i.p.)</th>
<th>Mean rise in temperature (± SE of the mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td>-</td>
<td>1.01 ± 0.04</td>
</tr>
<tr>
<td>L-dopa</td>
<td>100mg/kg</td>
<td>-0.01 ± 0.084</td>
</tr>
<tr>
<td></td>
<td>200mg/kg</td>
<td>-0.03 ± 0.094</td>
</tr>
<tr>
<td>Apomorphine</td>
<td>5mg/kg</td>
<td>0.28 ± 0.084</td>
</tr>
<tr>
<td></td>
<td>10mg/kg</td>
<td>0.24 ± 0.044</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>5mg/kg</td>
<td>0.79 ± 0.073</td>
</tr>
<tr>
<td></td>
<td>10mg/kg</td>
<td>0.20 ± 0.083</td>
</tr>
<tr>
<td>SK &amp; F 38393</td>
<td>5mg/kg</td>
<td>0.48 ± 0.033</td>
</tr>
<tr>
<td></td>
<td>10mg/kg</td>
<td>0.20 ± 0.083</td>
</tr>
<tr>
<td>Pimozide</td>
<td>0.5mg/kg</td>
<td>1.0 ± 0.18 NS</td>
</tr>
<tr>
<td>L-dopa + Pimozide</td>
<td>100mg/kg</td>
<td>0.70 ± 0.133</td>
</tr>
<tr>
<td></td>
<td>200mg/kg</td>
<td>0.79 ± 0.073</td>
</tr>
<tr>
<td>Apomorphine + Pimozide</td>
<td>5mg/kg</td>
<td>1.01 ± 0.023</td>
</tr>
<tr>
<td></td>
<td>10mg/kg</td>
<td>0.90 ± 0.123</td>
</tr>
<tr>
<td>SK &amp; F 38393 + Pimozide</td>
<td>10mg/kg</td>
<td>1.22 ± 0.19 NS</td>
</tr>
<tr>
<td>Amphetamine + Pimozide</td>
<td>5mg/kg</td>
<td>1.16 ± 0.12 NS</td>
</tr>
</tbody>
</table>

1. TAB vaccine was administered. The mean rise in rectal temperature ascertained at 2 hours.
2. Drug administered in saline at the time of administration of the pyrogen.
3. Value differs significantly (P<0.05) from that for control.
4. Reduction in temperature.
Table - 15

**Effect of dopamine receptor stimulant and blockers on the body temperature of rats**

Temperature changes + Mean ± SE in °C

<table>
<thead>
<tr>
<th></th>
<th>Dopamine</th>
<th>Apomorphine</th>
<th>Amphetamine</th>
<th>SK &amp; F 38393</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control Hypothermia</td>
<td>1.84 ± 0.22 (5)</td>
<td>1.69 ± 0.07 (8)</td>
<td>0.47 ± 0.01 (4)</td>
<td>0.77 ± 0.06 (5)</td>
</tr>
<tr>
<td>After rise</td>
<td>No change (5)</td>
<td>No change (5)</td>
<td>0.77 ± 0.15 (4)</td>
<td>No change (5)</td>
</tr>
<tr>
<td>After Pimozide Hypo.</td>
<td>0.54 ± 0.22(\times) (5)</td>
<td>0.53 ± 0.17(\times) (5)</td>
<td>0.14 ± 0.02(\times) (5)</td>
<td>0.44 ± 0.11 (5)</td>
</tr>
<tr>
<td>20 ug/kg</td>
<td>No change (5)</td>
<td>No change (5)</td>
<td>1.00 ± 0.24 (5)</td>
<td>- (8)</td>
</tr>
<tr>
<td>After Haloperidol 4 mg/kg</td>
<td>1.00 ± 0.28 (5)</td>
<td>0.73 ± 0.2 (5)</td>
<td>0.78 ± 0.23 (5)</td>
<td>0.66 ± 0.22</td>
</tr>
<tr>
<td></td>
<td>No change</td>
<td>No change</td>
<td>1.00 ± 0.24 (5)</td>
<td>No change (5)</td>
</tr>
</tbody>
</table>

Figure in parenthese represent number of observations.

\(\times\) = \(P < 0.05\)

\(\times\times\) = \(P < 0.001\)
after 7 days saline administration, fell down to 4.13±0.7t (P<0.05) after the administration of SK & F 38393, 1mg/kg, i.p. daily for 7 days. At the dose of 5mg/kg, i.p. for 7 days there was a decrease in body weight (5.35±0.64; P<0.001). In these doses the drug did not produce any apparent change in behaviour or motor activity, viz stereotype behaviour. Pimozide (0.5mg/kg, i.p.), a specific dopamine receptor blocking agent did not have any effect on the food consumption, this dose also did not produce any apparent neuroleptic activity viz. catalepsy or ptosis but it completely abolished the reduction in food intake induce by SK & F 38393 (Table 16).

Oral administration of SK & F 38393 at the doses of 5mg/kg daily for 10 days also produced significant decrease in the body weight when food and water were allowed ad libitum. The mean increase in body weight was 13.6±2.2g after 10 days oral saline treatment. After SK & F 38393 5mg/kg orally for 10 days. There was a mean decrease in body weight of 4.54±0.0039 (P<0.001). Ten days after the withdrawal of the drug and increase in body weight was observed (mean 12.31±2.69g; P<0.01). No significant change in S.M.A. was observed. S.M.A. was also not significantly affected after administration of SK & F 38393 5mg/kg i.p.
### Decreased food intake induced by SK & F 38393 in albino rats and its reversal by pimozide

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose (mg/kg, i.p.)</th>
<th>No. of Animals</th>
<th>Food consumption of g/100g of body weight ± SE</th>
<th>% Change and significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td>-</td>
<td>7</td>
<td>16.98 ± 1.75</td>
<td>-</td>
</tr>
<tr>
<td>SK &amp; F 38393</td>
<td>1.0</td>
<td>5</td>
<td>11.18 ± 0.35</td>
<td>34.15 P &lt; 0.01</td>
</tr>
<tr>
<td>SK &amp; F 38393</td>
<td>5.0</td>
<td>5</td>
<td>6.15 ± 1.01</td>
<td>63.78 P &lt; 0.001</td>
</tr>
<tr>
<td>Pimozide</td>
<td>0.5</td>
<td>5</td>
<td>15.44 ± 0.24</td>
<td>No significant</td>
</tr>
<tr>
<td>Pimozide + SK &amp; F 38393</td>
<td>0.5+5.0</td>
<td>5</td>
<td>15.63 ± 2.40</td>
<td>Not significant</td>
</tr>
</tbody>
</table>
Food intake:

Apomorphine (5mg/kg i.p.), Levo-dopa (200mg/kg i.p.) and amphetamine (5mg/kg i.p.) reduced the food intake significantly (P<.01, P<.001 and P<.001 respectively) in rats (Table 17) associated with decrease in body weights.

Pimozide (0.5mg/kg i.p.) did not produce any effect of its own, on food intake or neuroleptic activity viz catalepsy or ptosis. It however, completely abolished the reduction in food intake, induced by dopaminergic agonists i.e. amphetamine, apomorphine and L-dopa (Table 17). Further in our study another dopamine receptor blockers haloperidol (4mg/kg) also abolished significantly the reduction in food intake induced by dopaminergic agonists. Adrenergic and serotonergic blockers were not able to alter the food intake.

Drinking behaviour in rats:

It was observed in our study that there was no significant change in water intake in control group following i.c.v. administration of normal saline (Table 18). However i.c.v. dopamine in a dose of 100 μg significantly (P<0.001) increased the water intake. Furthermore apomorphine (100 μg; P<.01) and SK & F 38393 (P<0.05) also significantly increased the water intake.
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose (mg/kg)</th>
<th>Saline</th>
<th>Amphetamine (5mg/15g, i.p.)</th>
<th>Apomorphine (10mg/15g, i.p.)</th>
<th>Levo-dopa (200mg/15g, i.p.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Food consumption g/100g of body wt. + SE</td>
<td>% Change and significance</td>
<td>Food consumption g/100g of body wt. + SE</td>
<td>% Change and significance</td>
</tr>
<tr>
<td>Saline</td>
<td>-</td>
<td>14.23±1.17</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Control</td>
<td>-</td>
<td>-</td>
<td>7.98±0.51 P&lt;.001</td>
<td>0.69±1.14 P&lt;.001</td>
<td>10.468±0.77 P&lt;.001</td>
</tr>
<tr>
<td>Pimozide</td>
<td>0.5mg/kg</td>
<td>13.53±.84 4.051(NS) 12.66±1.71</td>
<td>11.03(NS)</td>
<td>12.38±0.84 13.00(NS)</td>
<td>11.58±1.91 18.62(NS)</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>4mg/kg</td>
<td>13.76±.19 3.30 (NS) 12.4±0.79</td>
<td>12.86(NS)</td>
<td>14.52±2.86 2.03 (NS)</td>
<td>13.32±0.57 6.39(NS)</td>
</tr>
<tr>
<td>Cyproheptadine</td>
<td>4mg/kg</td>
<td>13.42±0.60 5.69(NS) 9.76±2.01</td>
<td>31.41 (P&lt;.001)</td>
<td>9.4±1.03 33.94 (P&lt;.001)</td>
<td>10.90±2.37 23.40 (P&lt;.001)</td>
</tr>
<tr>
<td>Priscol + Propranolol</td>
<td>4mg/kg + 2mg/kg</td>
<td>12.78±.24 14.40(NS) 9.61±0.98</td>
<td>32.46 (P&lt;.001)</td>
<td>9.76±2.01 31.41 (P&lt;.001)</td>
<td>9.77±2.01 31.34 (P&lt;.001)</td>
</tr>
</tbody>
</table>
Table - 18

Effect of i.c.v. dopamine, apomorphine and SKF 38393 and their modification by pimozide on water intake in rats:

<table>
<thead>
<tr>
<th>Drug (Dose i.c.v.)</th>
<th>Pretreatment (dose i.c.v.)</th>
<th>No. of Animals</th>
<th>Water intake (ml/100g/24h) before treatment</th>
<th>After treatment</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td>-</td>
<td>5</td>
<td>23.98 ± 0.31</td>
<td>23.48 ± 0.21</td>
<td>&gt; .05</td>
</tr>
<tr>
<td>Dopamine (100 µg)</td>
<td>-</td>
<td>5</td>
<td>22.66 ± 0.52</td>
<td>39.08 ± 1.37</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Pimozide (50 µg)</td>
<td>-</td>
<td>5</td>
<td>26.64 ± 0.91</td>
<td>27.48 ± 0.60</td>
<td>&gt; .05</td>
</tr>
<tr>
<td>Dopamine (100 µg)</td>
<td>Pimozide (50 µg)</td>
<td>5</td>
<td>19.8 ± 1.08</td>
<td>20.0 ± 1.02</td>
<td>&gt; .05</td>
</tr>
<tr>
<td>Apomorphine (100 µg)</td>
<td>-</td>
<td>5</td>
<td>16.32 ± 1.30</td>
<td>19.70 ± 2.11</td>
<td>&lt; .01</td>
</tr>
<tr>
<td>Apomorphine (100 µg)</td>
<td>Pimozide (50 µg)</td>
<td>5</td>
<td>16.72 ± 0.72</td>
<td>16.50 ± 0.48</td>
<td>&gt; .05</td>
</tr>
<tr>
<td>SK &amp; F 38393 (100 µg)</td>
<td>-</td>
<td>20</td>
<td>47.93 ± 16.23</td>
<td>42.75 ± 6.30</td>
<td>&lt; .01</td>
</tr>
<tr>
<td>SK &amp; F 38393 (100 µg)</td>
<td>Pimozide (50 µg)</td>
<td>20</td>
<td>40.77 ± 6.73</td>
<td>57.50 ± 9.75</td>
<td>&lt; .05</td>
</tr>
</tbody>
</table>
Pimozide (50 μg i.c.v.) per se had no significant effect on water intake but it blocked the excitatory effects of dopamine apomorphine and of SK & F 38393 on water intake as subsequent administration of dopaminergic drugs failed to produce significant change in water intake (Table-18).

**Effect on morphine-induced analgesia in rat:**

Dopamine agonists and antagonists did not exhibit analgesic activity when tested by Bianchi's tail clip method. However these drugs altered morphine induced analgesia by thermal method.

**Effect of L-dopa:**

L-dopa in doses of 100mg/kg, 200mg/kg, and 300mg/kg body weight produced significant increase in reaction time as compared to normal reaction time (i.e. without drug treatment) in the same animals. Results are depicted in Fig. 15. The increase in reaction time produced by L-dopa was found to be dose dependent. The maximum effect was observed at 15 and 30 minutes after drug administration.

With levo-dopa, in the doses of 100mg/kg, 200mg/kg and 300mg/kg, i.p. mean reaction time from control value at 3.0, 3.1 and 2.8 (n=9) was significantly increased after 15, 30, 45 and 60 minutes (P<0.0001).
Figure 15: ANALGESIOMETRY IN RATS BY TALL-FLICK METHOD

(DRUGS INJECTION I.P.)

(A) Dose dependent analgesic effect of SK & F 38393 injection i.p. in rats (n=9).

(B) Showing the antinociceptive effect of pimozide. Did not produce significant alteration in the reaction time of L-dopa, SK & F 38393 and Apomorphine (n=9).

(C) Dose dependent analgesic activity of L-dopa (100, 200 and 300mg/kg/i.p.) (n=9).

(D) Dose dependent analgesic activity of the apomorphine (2.5, 5 and 10mg/kg, i.p.) (n=9).

Ordinates: percent increase in the mean reaction time
Abscissa: Time in minutes after i.p. injection.
Levo-dopa, when given along with morphine (5 mg/kg i.p.) was found to enhance the analgesic activity of morphine (n=3) (P < 0.001).

**Effect of apomorphine:**

Apomorphine showed analgesic activity in the doses at 2.5 mg/kg, 5 mg/kg, and 10 mg/kg when given by i.p. injection. The analgesic effect was dose-dependent (P < 0.001) (Fig. 15). Apomorphine when given along with morphine (5 mg/kg i.p.) was found to enhance morphine-induced analgesia. (Fig. 16C).

**Effect of SK & F 38393:**

SK & F 38393, a newer dopamine agonist, in the doses at 2.5 mg/kg, 5 mg/kg, and 10 mg/kg produced dose-dependent analgesic effect (Fig. 15). SK & F 38393 when given along with morphine (5 mg/kg i.p.) was found to enhance morphine-induced analgesia. (Fig. 16A).

**Effect of Pimozide:**

Pimozide, a specific blocker of DA receptors, in the dose of 0.5 mg/kg i.p. was not found to possess any analgesia activity of its own. However, pretreatment with pimozide in L-dopa, SK & F 38393 and apomorphine treated rats did not produce significant alteration in the reaction time as compared to control. It was found to reduce the analgesic effect of morphine (Fig. 16A, 16B, 16C).
FIGURE 16: Effect of dopaminergic drugs on the analgesic effect of morphine (5mg/kg, i.p.) measured by tail flick method (Analgesiometer; Techno).

(A) Note pimozide (0.5mg/kg, i.p.) antagonises morphine analgesia and SK & F 38393 (2.5 & 5 mg/kg, i.p.) in contrast increases morphine analgesia.

(B) Note pimozide (0.5mg/kg, i.p.) antagonises morphine analgesia and dopa in contrast shows dose dependent (100, 200 and 300mg/kg, i.p.) increase in morphine analgesia.

(C) Note pimozide (0.5mg/kg, i.p.) antagonises morphine analgesia and apomorphine (2.5, 5 and 10 mg/kg, i.p.) in contrast increase morphine analgesia.
Fig. 16

A

- - - - SALINE
- - - - MORPHINE 5 mg/kg
- - - - MORPHINE + PIMOZIDE
- - - - SK & F 5 mg/kg + MORPHINE
- - - - SK & F 5 mg/kg + MORPHINE

% CHANGE IN REACTION TIME (SEC)

0 15 30 45 60 TIME IN MINUTES

B

- - - - SALINE
- - - - MORPHINE 5 mg/kg
- - - - PIMOZIDE 0.5 mg/kg + MORPHINE
- - - - LEVODOPA 200 mg/kg + MORPHINE 5 mg/kg
- - - - LEVODOPA 300 mg/kg

C

- - - - SALINE
- - - - MORPHINE 5 mg/kg + PIMOZIDE 0.5 mg/kg + MORPHINE
- - - - APOMORPHINE 5 mg/kg + MORPHINE 10 mg/kg
- - - - APOMORPHINE 5 mg/kg + MORPHINE 10 mg/kg

TIME IN MINUTES

0 15 30 45 60
Effect of dopaminergic agents on acetic acid induced writhing in mice:

It was observed that in the control group which received only normal saline (10ml/mg i.p.) as the test drug, the average number of writhes for 50 minutes were 32.4±2.55 (Table-19). When L-dopa (200mg/kg), apomorphine (5mg/kg) and SK & F 38393 (5mg/kg) was used as the test drugs, the average number of writhing episodes were reduced to 3.16±1.19, 5.4±0.8 and 2.7±0.88, respectively and thus it provided protection against the acetic acid induced writhing. Pimozide as such had no significant effect on writhing but pretreatment with pimozide inhibited the protection of acetic acid induced writhing produced by L-dopa, apomorphine and SK & F 38393 (Table-19).

Role of dopamine in morphine addiction:

The study was conducted in two parts each having its own control. The effect of the pretreatment with the various drugs on naloxone induced withdrawal counted and signs have been shown in Table (Table-20).

The dopamine agonists i.e., apomorphine, d-amphetamine, L-dopa and SK & F 38393 increased the jumping scores while "wet dog shaking" and "writhing" scores were lowered in most cases with the exception that wet dog shaking score was increased in apomorphine and writhing was more in L-dopa treatment. The checked signs "scream on touch" and "hostility on handling" were not affected by dopamine like drugs.
Effect of DA agonist and antagonist on acetic acid induced stretching episodes in mice
(values are mean ± SE number of observation in parenthesis):

<table>
<thead>
<tr>
<th>Group</th>
<th>Dose in mg/kg, i.p.</th>
<th>Stretching episodes for 30 min.</th>
<th>% inhibitory activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (10)</td>
<td>-</td>
<td>32.4 ± 2.35</td>
<td></td>
</tr>
<tr>
<td>L-dopa (10)</td>
<td>200 mg/kg</td>
<td>3.18 ± 1.19**</td>
<td>90.24</td>
</tr>
<tr>
<td>Apomorphine (10)</td>
<td>5 mg/kg</td>
<td>3.5 ± 0.8**</td>
<td>89.19</td>
</tr>
<tr>
<td>SK &amp; F 38393 (10)</td>
<td>5 mg/kg</td>
<td>2.7 ± 0.88**</td>
<td>91.66</td>
</tr>
<tr>
<td>Pimozide (6)</td>
<td>0.5 mg/kg</td>
<td>40.16 ± 8.19</td>
<td></td>
</tr>
<tr>
<td>Pimozide + L-dopa (6)</td>
<td>0.5 mg/kg + 200 mg/kg</td>
<td>26.00 ± 4.46*</td>
<td>19.85</td>
</tr>
<tr>
<td>Pimozide + Apomorphine (6)</td>
<td>0.5 mg/kg + 5 mg/kg</td>
<td>32.16 ± 1.03</td>
<td></td>
</tr>
<tr>
<td>Pimozide + SK &amp; F 38393 (6)</td>
<td>5 mg/kg + 5 mg/kg</td>
<td>39.66 ± 1.10</td>
<td></td>
</tr>
</tbody>
</table>

* P < 0.05
** P < 0.001
Catecholamine depletion, i.e., reserpine decreases the occurrence of all the counted and checked signs. Furthermore, it was also observed that pimozide pretreatment totally abolished the jumping response, but mepyramine (4mg/kg), cyproheptadine (4mg/kg) treatment failed to antagonize the jumping response or other withdrawal signs, whereas imipramine, an uptake-1 blocker increased the jumping response, wet dog shaking, but writhing remain unaffected (Table-20).

Effect of morphine-dependence:

As shown in table-21, drugs acting through dopaminergic mechanism were studied in mice chronically treated with morphine (5mg/kg, i.p.). In a "2 day test" in mice, levodopa (total dose = 1000mg/kg), amphetamine (total dose 10mg/kg) and apomorphine (total dose 5mg/kg) were found to increase the jumping response precipitated by nalorphine (n=10). Nalorphine HCl (40mg/kg, i.p.) precipitated the jumping responses in morphine-dependent mice. The intensity of this response was diminished when the animals dependent on morphine were challenged with pimozide (total dose = 0.5mg/kg). The incidence of counted withdrawal sign was compared to morphine treated mice (Table-21). Further when mice are treated with reserpine (5mg/kg, i.p.) also decreased the jumping response but imipramine (total dose 10mg/kg) and cyproheptadine (4mg/kg) failed to protect the animals against the withdrawal symptom.
The influence of certain drugs on naloxone induced withdrawal syndrome in groups of morphine dependent rats:

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Jumping</th>
<th>Writhing</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naloxone</td>
<td>50 ± 6.91</td>
<td>6.4 ± 1.32</td>
<td></td>
</tr>
<tr>
<td>Apomorphine + Naloxone</td>
<td>81 ± 8.13**</td>
<td>9.4 ± 0.74 N.S.</td>
<td></td>
</tr>
<tr>
<td>d-Amphetamine + Naloxone</td>
<td>103 ± 7.44***</td>
<td>8 ± 0.31 N.S.</td>
<td></td>
</tr>
<tr>
<td>Levodopa + Naloxone</td>
<td>129.6 ± 7.49***</td>
<td>14.6 ± 0.93*</td>
<td></td>
</tr>
<tr>
<td>SK &amp; F 38393 + Naloxone</td>
<td>86.25 ± 26.44**</td>
<td>5.4 ± 1.12 N.S.</td>
<td></td>
</tr>
<tr>
<td>Pimozide + Naloxone</td>
<td>1.2 ± 0.96***</td>
<td>2.2 ± 1.07</td>
<td></td>
</tr>
<tr>
<td>Cyproheptadine + Naloxone</td>
<td>48.6 ± 3.66 N.S.</td>
<td>5.4 ± 0.51 N.S.</td>
<td></td>
</tr>
<tr>
<td>Mepyramine + Naloxone</td>
<td>44.4 ± 4.48 N.S.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reserpine + Naloxone</td>
<td>8.0 ± 4.35*</td>
<td>2.2 ± 1.07</td>
<td></td>
</tr>
<tr>
<td>Impramine + Naloxone</td>
<td>193.07 ± 62.20***</td>
<td>0.25 ± 2.50</td>
<td></td>
</tr>
</tbody>
</table>

* P < 0.05
** P < 0.01
*** P < 0.001
The influence of dopamine agonists and antagonists on nalorphine induced withdrawal (Two days test)

<table>
<thead>
<tr>
<th>No.</th>
<th>Drug</th>
<th>Total dose</th>
<th>Average jumping</th>
<th>No. of mice jumped/No tested</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>mp/kg, i.p.</td>
<td>per mouse</td>
<td></td>
</tr>
<tr>
<td>1.</td>
<td>Control (Saline)</td>
<td>0.2 ml/20gm</td>
<td>0</td>
<td>0/10</td>
</tr>
<tr>
<td>2.</td>
<td>Morphine</td>
<td>400</td>
<td>29.5 ± 1.10</td>
<td>10/10</td>
</tr>
<tr>
<td>3.</td>
<td>Levodopa + Morphine</td>
<td>1000 + 400</td>
<td>38.6 ± 6.20</td>
<td>8/10</td>
</tr>
<tr>
<td>4.</td>
<td>Amphetamine + Morphine</td>
<td>10 + 400</td>
<td>36.6 ± 3.9</td>
<td>9/10</td>
</tr>
<tr>
<td>5.</td>
<td>Apomorphine ± Morphine</td>
<td>5 + 400</td>
<td>31.3 ± 5.2</td>
<td>8/10</td>
</tr>
<tr>
<td>6.</td>
<td>Pimozide + Morphine</td>
<td>0.5 + 400</td>
<td>8.4 ± 5.33</td>
<td>2/10</td>
</tr>
<tr>
<td>7.</td>
<td>Pimozide + Levodopa + Morphine</td>
<td>0.5 + 1000 + 400</td>
<td>17.8 ± 7.11</td>
<td>4/10</td>
</tr>
<tr>
<td>8.</td>
<td>Apomorphine + Pimozide + Morphine</td>
<td>0.5 + 5 + 400</td>
<td>8.5 ± 7.85</td>
<td>2/10</td>
</tr>
<tr>
<td>9.</td>
<td>Reserpine + Morphine</td>
<td>5 + 400</td>
<td>9.6 ± 8.03</td>
<td>1/5</td>
</tr>
<tr>
<td>10.</td>
<td>Imipramine + Morphine</td>
<td>10 + 400</td>
<td>41.0 ± 4.44</td>
<td>9/10</td>
</tr>
<tr>
<td>11.</td>
<td>Cyproheptadine + Morphine</td>
<td>4 + 400</td>
<td>42.0 ± 3.99</td>
<td>4/5</td>
</tr>
</tbody>
</table>
Effect of levo-dopa, dopamine and SK & F 38393 with blood glucose level:

Intravenous injection of L-dopa, dopamine and SK & F 38393 evoked a clear and marked hyperglycaemic response. Administration of L-dopa, 200mg/kg, dopamine 20mg/kg and SK & F 38393 5mg/kg caused increase in the blood glucose level. The response to L-dopa was, however, more prolonged than that of dopamine as shown in Fig.17A.

As may be seen from Fig.17A the maximal response following intravenous L-dopa, dopamine injection was observed at 30 minutes. The effect was decreased after 60 minutes whereas L-dopa and dopamine induced hyperglycaemia still persisted. The maximal hyperglycaemia following these drugs occurred at 30 minutes when the animals are pretreated with pimozide 1mg/kg, it antagonised the hyperglycaemic action of dopamine, apomorphine and L-dopa. Pimozide had no marked effect of its own on blood glucose level as compared to control value (Fig.19). Further nialamide potentiated the hyperglycaemic effect of L-dopa (Fig.17B). Identical results were also observed with dopamine + nialamide.

The question whether the hyperglycaemic effect of L-dopa, dopamine, and SK & F 38393 was primarily on the liver or on the pancreas was approached in several ways. Injection of dopamine, L-dopa or SK & F 38393 in alloxan diabetic mice did not evoke any hyperglycaemia (Table-22).
Figure 17: EFFECT OF NIALAMIDE AND PIMOZIDE ON HYPERGLYCAEMIA INDUCED BY DOPAMINE AND L-DOPA IN MICE:

(A) Changes in blood glucose level at 0 (Control), 30 minutes and 60 minutes following intravenous injection of L-dopa (200mg/kg) and dopamine (20 mg/kg). Each point represents mean ± SE (n=6).

Note pimozide (1mg/kg, i.p.) administered before 1 hour inhibits the L-dopa and dopamine induced hyperglycaemia.

(B) Note the potentiation of L-dopa (200mg/kg, i.p.) induced hyperglycaemia by pretreatment with nialamide (50mg/kg/i.p.) 1 hr prior to L-dopa injection.

Each point represents mean ± SE (n=8).
FIG. 17(A)

MEAN BLOOD GLUCOSE mg/dl

TIME IN MINUTES

DOPAMINE 10 mg/kg
L-DOPA 200 mg/kg
L-DOPA + PIMOXIDE
CONTROL
DOPAMINE + PIMOXIDE
PIMOXIDE 1 mg/kg
FIG. 17 (B)

L-DOPA 200 mg/kg
NIALAMIDE 50 mg/kg

L-DOPA 200 mg/kg

CONTROL
NIALAMIDE 50 mg/kg

TIME IN MINUTES
Table - 22

The protective effects of pimozide against the action of alloxan on albino rats

<table>
<thead>
<tr>
<th>Normal Alloxan Control (Group-A)</th>
<th>Alloxan Controls (24h) (Group-B)</th>
<th>Pimozide protected alloxan animals (24h) (Group-C)</th>
<th>Alloxan Controls (4 days) (Group-D)</th>
<th>Pimozide alloxan animal (4 days) (Group-E)</th>
<th>P.Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Sugar</td>
<td>93.3±2.1</td>
<td>373.5±20.9</td>
<td>356.4±6.10</td>
<td>114.0±11.7</td>
<td>320±15.9</td>
</tr>
<tr>
<td>(mg%)</td>
<td>(20)</td>
<td>(5)</td>
<td>(8)</td>
<td>(5)</td>
<td>(20)</td>
</tr>
</tbody>
</table>

Remarks: Data represents mean ± SE

Figure in parenthese represent number of observations

NS: Not significant
Glabenclamide was injected intravenously 5 minutes before or 5 minutes after intravenous administration of dopamine when glabenclamide was given 5 min. prior to dopamine the usual hyperglycaemic response was obtained but when glabenclamide was given after dopamine no hyperglycaemia was observed (Fig. 18).
Figure 18: EFFECT OF GLABENCLAMIDE ON DOPAMINE INDUCED HYPERGLYCAEMIA IN MICE:

DA = Dopamine 40mg/kg injection i.v.
GC = Glabenclamide 10mg/kg i.v.
DA = DA induced hyperglycaemia
DA+ = GC 5 min. after DA.
GC
DA− = DA induced hyperglycaemia
GC+DA = GC 5 min. before DA supresses DA induced hyperglycaemia

Each bar represents mean ± SE (n=5), *P < 0.001 column 4 compared to column 3.
Figure 19: INTERACTIONS OF DOPAMINE AGONISTS (Apomorphine, L-dopa and Amphetamine) AND PIMOZIDE ON BLOOD SUGAR LEVEL OF RATS.

Each point shows effect of pimozide on the increased blood sugar level induced by i.p. injection of apomorphine, L-dopa and amphetamine (n=5).
Fig. 19

- CONTROL
- PIMOZIDE 1 mg/kg
- APOMORPHINE 5 mg/kg
- APOMORPHINE 5 mg/kg + PIMOZIDE
- L-DOPA 200 mg/kg
- L-DOPA 200 mg/kg + PIMOZIDE 1 mg/kg
- AMPHETAMINE 5 mg/kg
- AMPHETAMINE 5 mg/kg + PIMOZIDE 1 mg/kg

MEAN BLOOD SUGAR LEVEL mg/dl

TIME IN HOURS

1 2 3