AN OUTBREAK OF ATROPINE POISONING

BY

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Fifteen men, all Royal Air Force personnel, varying in age from nineteen to forty-two years, but mainly in the early twenties, were given a period of prolonged narcosis intended to last ten days in each case. They were all in satisfactory physical health but suffered from psychoneuroses.

The technique of treatment was a modification of that advocated by Brody (1940) for restless, older patients: 3 gr. of dial twice a day, together with paraldehyde in 3 drachm doses to a maximum of 9 drachms daily. To offset vomiting, 1 minim of liquor atropine is suspended in each 1-5 drachms of paraldehyde, thus giving a maximum of 6 minims of liquor atropine daily, which Brody states may be maintained for several days. He reported that fifteen of twenty-one patients vomited without atropine and only twenty-one of sixty-nine with atropine. From his description of the daily incidence of the minor complications which developed, it appears that vomiting, pyrexia, and albuminuria were evenly distributed throughout the treatment, whereas restlessness was more frequent in the second week, with fifty-three restless days to sixteen in the first week. The facts to be reported suggest that this restlessness is an atropine symptom, and it is possible that in some of Brody's cases more serious poisoning was escaped by a hair's breadth.

In this series, before some patients had finished the course and at the commencement of the treatment in others, the dose of atropine recommended by Brody was doubled because vomiting persisted. The doctor in charge of the treatment left before the narcotics were completed and the present writer took over, unfortunately unaware that any atropine was being used, and believing the drugs employed to be paraldehyde and dial only. As patients came out of the narcosis, several developed severe reactions and there appeared to be an epidemic of schizophrenia. Cases of atropine poisoning reported from time to time are usually concerned with the effects of a single large dose. Here the dosage was cumulative and spread over several days, and symptomatology was complicated by the simultaneous administration of large doses of dial and paraldehyde. The amounts of atropine taken are shown in the Table.

Combining these results with those previously reported by Brody, one can state tentatively that 6-0 minims of the liquor (equivalent to 4-0 gr. atropine sulphate) can be given daily, for ten to fourteen days at least, without symptoms of any gravity developing, yet a dose of 8-8 minims (equivalent to 6-0 gr. atropine sulphate) daily for ten days may endanger life. This is a very low margin of safety. A dosage of 94 minims (nearly 1-0 gr. atropine sulphate) in ten days produced severe symptoms, but with no threat to existence. The smallest total dose to produce hallucinosis was 40 minims.

Progress of the Narcosis

Taken on the whole, the progress of the narcosis was very smooth. Certain symptoms are described below, but they should be interpreted against the background of an easily manageable treatment. Only two patients vomited, one on the second day and another on the ninth and tenth days of

Dosage Table

<table>
<thead>
<tr>
<th>Case</th>
<th>Total Liq. atropine (in minims)</th>
<th>No. of days treated</th>
<th>Average daily dose (in minims)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very severely affected</td>
<td>1</td>
<td>88</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>84</td>
<td>10</td>
</tr>
<tr>
<td>Severely affected</td>
<td>3</td>
<td>56</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>94</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>96</td>
<td>10</td>
</tr>
<tr>
<td>Hallucinated</td>
<td>6</td>
<td>58</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>68</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>40</td>
<td>5</td>
</tr>
<tr>
<td>Unduly restless</td>
<td>9</td>
<td>66</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>80</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>50</td>
<td>6</td>
</tr>
<tr>
<td>Possibly showing atropine effects</td>
<td>12</td>
<td>58</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>68</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>42</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>30</td>
<td>4</td>
</tr>
</tbody>
</table>
treatment. All patients had 6 gr. of dial every day, and the average daily dose of paraldehyde was about 9 drachms, the average sleep for the group being eighteen hours in every twenty-four. The average daily intake of nutrient fluid was 136 oz., and the average daily amount of urine excreted, excluding days when there was incontinence, was 87 oz. The blood pressure was taken daily and a typical variation was between 105 and 120 mm. Hg systolic, and between 60 and 80 diastolic. In one man only, when the blood pressure was 85 mm. Hg systolic and 50 diastolic, did symptoms of a minor collapse appear, but he responded well to treatment. One patient had retention which did not need catheterization, one patient had an attack of hiccoughs, and two complained of headache. One man made repeated complaints of chilliness. There were no high temperatures, but about half the patients recorded 99° F. or 100° F. on a few occasions.

These symptoms are common to prolonged sleep treatment. The following symptoms and signs, viewed in retrospect, are more likely to have been due to atropine.

**Atropine Effects during Narcosis**

The most striking and prominent effects were restlessness and a peculiar emotionalism. The restlessness was usually combined during the waking hours with frequent attempts to get out of bed, garrulity, and occasional noisiness and excitement. It was seen in eight cases, developing round about the sixth day or earlier and usually continuing to the end, being chiefly noticeable in contrast to the preceding apathy. Towards the eighth day increasing confusion and irrationality were occasionally noticed. The emotionalism was remarkable for the frequency with which it was associated with facile cheerfulness; it was encountered in at least six men, in two of whom it increased to awkward hilarity. This good humour developed between the fifth and ninth days except in the two hilarious men (who were sometimes convulsed with laughter), in each of whom the symptom developed on the fourth day. In two cases fatuous amiability followed a few days of increased depression, and this in turn gave way before the end of treatment to a disgruntled humour with aggression and refusal of food. Three more cases cried at times after the sixth day, and two became anxious. It will be clear that it is impossible to separate these symptoms entirely from the effects of narcosis, but their frequency and the clinical impression suggest atropinism.

Of the customary signs of atropine poisoning, the increased pulse rate was masked during the course of treatment, presumably by the action of the sedatives. The only unusual feature was the fluctuation in individual rates, a typical swing being between 55 and 85 per minute, without apparent reason. Two days after the cessation of treatment the pulse rate was usually about 80 to 100. Towards the end of the course there was occasionally a slight increase in the average pulse rate, taking the mean of slowest and fastest; for example in one case from 60, to 70, to 80 per minute on the eighth, ninth, and tenth days. A few patients were noticed to have dry and dirty mouths at the end of the treatment, but this was put down to the toxemia of narcosis; tongues were always moist from the second day after treatment. In two cases dilatation of the pupils was actually commented on at the bedside, but no significance was attached to this observation until it was recalled when atropine poisoning was diagnosed. In neither case was it continuous.

Two men complained of discomfort occasioned by a desire to micturate without being able to do so, and this has been described as an atropine effect (Clark, 1940). One man, who had slept about twenty-one hours daily for four days, only slept twelve hours daily during the next three days of treatment, although the dose of sedative was increased. The ward sister has since informed me that two men showed a hot, dry, skin for some days.

**Progress after the Narcosis**

The onset of the alarming aberrations occurred in a time sequence which was roughly similar in all those who developed urgent symptoms of acute mental disturbance. The first day after the suspension of treatment was reasonably quiet, but with a steady diminution of somnolence. During the second day the patient was wide awake, but disquieting behaviour was observed which rose to a peak during the third and fourth days, thereafter subsiding steadily. This finding is compatible with the comparatively rapid excretion of barbiturate and paraldehyde, leaving the more slowly excreted atropine to produce a purer effect.

The most striking early symptom was a pressure of talk accompanied by an irritable aggression and facile emotionalism, immoderate laughter being followed quickly by tears. Intermingled with evidence of increasing instability, there was a mixture of apprehension and anxiety. One patient revealed a hypomanic colouring in his symptoms, with flight and elation as well as volubility. On the fourth day after treatment this patient suddenly abandoned his unnatural good humour and became tremendously tense, excited, and pale with anger, speaking deliriously about the doctors and nurses. From the next day his excitement gradually subsided,
ATROPINE POISONING

exhibiting periodic effervescence of a kind to be described in further cases. Even after a week his behaviour and manner were odd. After that he became the pleasantly mannered youth, with disguised anxiety symptoms and a history of several years of psychopathic behaviour, whom we had known before the treatment. Another very similar case was transferred to a military mental hospital as a case of catatonic schizophrenia. He made a good recovery.

Three patients complained of considerable depression after treatment and one, the only death, after asserting that his thoughts were being read, fell thirty-five feet from his bedroom window and was killed. This may have been an accident, and a desire for air, an awkward window, and giddiness may have been responsible. Suicide is more likely, and he may have killed himself either because of his depression or in order to escape from atropine hallucinosis.

Dreams and nightmares were fairly common, and hallucinations of smell, hearing, and sight were noted—poisoned food, fire, and electric currents being prominent. In these states the anxiety and fear already referred to were exaggerated. Sometimes the dreams were distorted versions of recent terrifying experiences, and they were then probably the outcome of the anxiety, being similar to nightmares often observed in traumatic anxiety states.

Three patients had a strong craving for a cigarette soon after treatment and one of them had a distressing longing for sexual satisfaction. Giddiness was fairly common and with the first cigarette was excessive. It is difficult to assess these cravings, although the marked giddiness was probably an atropine effect. Only two patients complained of unsteadiness of gait, and in one this persisted for three days, but patients were mainly confined to bed. The first bowel action was sometimes painful, and one man, who had been given a dose of cascara, described it as “the worst agony I have ever experienced.” Four men complained of haziness of vision and inability to read or write. Three had headaches and spoke with difficulty, another could not find words, two were somewhat somnolent, and two commented on a sensation of peculiar blankness; in these it is almost impossible to differentiate between narcotic and atropine effects.

The very limited pulse range has already been commented upon. During the first four days after treatment there was a steady increase in the extent and duration of dilatation of the pupils, but in every case the dilatation was periodic, alternating with periods during which the pupils returned to normal size.

One case (case 1 of the Table) will be described separately because of the extraordinary resemblance of the severe symptoms to insulin coma. This patient was aged 19 and was suffering from acute anxiety after operational flying. On the eighth, ninth, and tenth days of narcosis treatment he was noticed to be confused and irrational when awake, and to be talking much disconnected nonsense. On the first day after treatment he was quiet and confused, muttering from time to time, but nothing was observed that gave rise to any anxiety. During the next day he had periods of restless excitement and began to complain that he was influenced by the rays of a wireless set and by the electric lights which played on him. During the periods of excitement his pupils were widely dilated, and sweating was marked. He continued to take fluids freely.

On the third day his hallucinatory experiences increased and he demonstrated invisible wounds and wiped imaginary blood from various places. At this time his continuing attacks of excitement were marked by obvious terror and apprehension, and in his more lucid moments he mentioned his dreams, which recalled his flying experiences. Between attacks the pupils were small. The pulse rate fluctuated between 80 and 120 per minute. During the third night he became delirious during his periodic attacks, and his pulse rate rose to 160, the temperature to 101°F, and the respiration rate to 25 per minute. He coughed up a little sputum, but the lungs were clear and the urine normal. By this time atropine poisoning had been diagnosed, and he was given morphia 0-25 gr., oxygen inhalations, and coramine injections, as well as ordinary nursing attention. On the fourth day his condition became much worse and his life was despaired of. He had successive attacks of coma, with a tremendous rise in the pulse rate to 180, 200, and over, until it became thready and uncountable. Respiration was coarse and rapid; the pupils dilated to the rims; drenching sweat poured from him, and he went into tonic rigidity and opisthotonus, with his legs extended and the arms flexed across his chest. This state was followed by jactitation of arms and head, after which he gradually relaxed, the pupils diminished to normal size, and he regained consciousness, with the pulse rate slowing and strengthening, the excessive perspiration being the last abnormality to diminish. The symptoms were exactly like hypoglycaemic coma with adrenaline crises. He was treated for shock, with warmth, elevation of the foot of the bed, coramine, and oxygen. On the advice of Air-Commodore Conybeare, intravenous salines were given and salt added to the diet. The patient took fluids well in his quieter periods throughout.

During the fifth day he had four more attacks, but each was less in intensity than the one before and the pulse rate rarely exceeded 160 per minute. The last attack worthy of the name occurred on the sixth day. Thenceforward he gradually recovered, except that on the fourteenth day after the narcosis treatment he displayed acute panic reaction after severe pain in the left side of the chest, which he interpreted as a dangerous heart attack.

Discussion

Clark (1940) states that atropine paralyses parasympathetic nerve endings by inhibiting acetylcholine, and that it has a variable stimulating action on the sympathetic, largely masked by the dominance of the action on the parasympathetic endings. Moderate doses produce cerebral stimulation, and there is stimulation of the lower motor centres of the brain. The action is known to be prolonged.

The dose of the liquor is 0-5 to 1 minim, that is 1/200 to 1/100 of a grain of atropine sulphate; 0-5 gr. has proved fatal, but, in a most exceptional
case, a dose of 15 gr. was survived. Susceptibility varies enormously. No case in this series had as much as 1 gr.

The acute signs and symptoms are dryness of the skin and secretions, dizziness, impaired vision, dilated pupils, and greatly increased pulse rate, with some increase in respiratory rate and a slight rise of temperature. Excitement, garrulity, and restlessness follow, and may lead on to delirium with hallucinations and finally coma. Epileptic attacks may occur, with paralysis of medullary centres. Munns (1929), writing of children under a month old, wonders if the heat-regulating centre is affected.

Young children are known to tolerate its action well, and sensitivity increases with age. Métivier (1935) describes an unusual reaction in a woman of seventy-four, who developed excitement and pleasing hallucinations after being given atropine eye drops. Carter (1940) describes the case of an old man of seventy-three who took 1·2 gr. of atropine. Treatment was not started for ten hours, when convulsions commenced. There was coma, dilated and fixed pupils, retention of urine, dry mouth, stertor, a rapid pulse, and spasticity and profuse perspiration. The spasticity is interesting in view of the rigidity in the attacks described above in Case 1 of the Table. Carter’s patient was persistently trying to get out of bed and was hallucinated, picking at the bed clothes and later complaining of blurred vision. On the second day he was elated, excited, very talkative, and complained of headache. He had recovered by the fourth day. Concerning the variation in pupillary size, it is interesting to recall the findings of Levine and Schilder (1942) in catatonics. After the instillation of atropine they noted in a proportion of these an inconstancy of pupillary reaction to light and before fixation, suggesting an autonomic imbalance with parasympathetic dominance.

In view of the comparative smallness of the dose of atropine in the cases reported here, and the fact that the prescription was spread over a period of up to ten days, the conclusion can hardly be escaped that the narcotic not only masked the action of the atropine effectively, but also in some way reduced its excretion, so that at the end of treatment an effect was rapidly produced as if something like the total atropine given was acting as a single dose. There was no evidence of renal damage, but there may have been selective changes in kidney function. The striking nature of the parasympathetic—sympathetic swings, which gradually grew in intensity following the cessation of treatment, suggest a “blocking” of hypothalamic cells with dial, followed by a sudden invasion by atropine as the dial was excreted.

Mental illnesses indistinguishable from schizophrenia have been produced by the events here described. These cases closely simulated catatonic excitement, and four cases showed the almost pathognomonic “thought reading and influence by external agencies” of schizophrenia. Daube (1942) has described four cases of “pervitin” psychosis with a general picture of paranoid ideas, illusions, hallucinations, restlessness, irritability, and pronounced anxiety. Some patients were euphoric. These symptoms are similar to those described in the present paper, and suggest a non-specificity in the causal agents which, acting on cortex or midbrain, or both, can produce schizophrenia-like reactions. Ivy and Goetzl (1943) also have described the excitement produced by “pervitin,” a benzedrine-like substance. The strong resemblance to schizophrenia produced by mescaline intoxication which was described by Stockings (1940) is closely paralleled by the cases described in this paper. The cortical effects of atropine must not be forgotten, but it is tempting to postulate that the dial facilitated a preponderating effect on the hypothalamus. The autonomic disturbances, and the unusual resemblance to insulin coma in one case, suggest a hypothalamic intoxication producing an illness indistinguishable from some forms of schizophrenia. Insulin acts primarily on the parasympathetic, presumably causing a pendulum over-action of the sympathetic and waves of adrenaline secretion. Here the parasympathetic may be paralysed, possibly freeing the sympathetic, or the actual hypothalamic cells may be disturbed in their action.

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