THE EPHEDRINE TREATMENT OF NOCTURNAL ENURESIS.

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Treatments for enuresis have been legion, but several authors have recorded beneficial results from the use of ephedrine hydrochloride.

**Table 1.—Summary from Literature.**

<table>
<thead>
<tr>
<th>Author</th>
<th>Numbers</th>
<th>Ages in years</th>
<th>Dose</th>
<th>Additional treatment</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parkhurst</td>
<td>10-12</td>
<td>10-12</td>
<td>$\frac{1}{2}$ gr. ($0.16$ gm.)</td>
<td>Limitation of fluids</td>
<td>“ Almost specific.”</td>
</tr>
<tr>
<td>Christopherson and Broadbent</td>
<td>12</td>
<td>3-13</td>
<td>$\frac{1}{2}$ gr. ($0.16$ gm.)</td>
<td>$\frac{1}{2}$ gr. ($0.25$ gm.) belladonna</td>
<td>4 controlled.</td>
</tr>
<tr>
<td>Brookfield</td>
<td>32</td>
<td>Children</td>
<td>$\frac{1}{2}$–5 gr. ($0.16–2.5$ gm.)</td>
<td>...</td>
<td>10 ceased.</td>
</tr>
<tr>
<td>Browne and Ford-Smith</td>
<td>6</td>
<td>14-20</td>
<td>1-4 gr. ($0.16–2.5$ gm.)</td>
<td>...</td>
<td>3 better; 2 worse.</td>
</tr>
<tr>
<td>Stalker and Band</td>
<td>27</td>
<td>Adults</td>
<td>$\frac{1}{2}$–3 gr. ($0.16–2.5$ gm.)</td>
<td>Limitation of fluids</td>
<td>8 ceased;</td>
</tr>
<tr>
<td>Kittredge and Brown</td>
<td>25</td>
<td>Children</td>
<td>$\frac{1}{2}$ gr. ($0.16$ gm.)</td>
<td>Less</td>
<td>3 better; 2 worse.</td>
</tr>
</tbody>
</table>

Total 102

Improved 85 (83.4%)  

Parkhurst's subjects urinated normally before and two hours after going to bed.

Christopherson and Broadbent report that of the 8 cases controlled by ephedrine $\frac{1}{2}$ ($0.16$ gm.), 7 were also controlled by gr. $\frac{1}{2}$ ($0.32$ gm.) pseudo-ephedrine hydrochloride, the eighth being controlled by gr. $\frac{1}{2}$ ($0.16$ gm.). Of the four cases requiring gr. $\frac{1}{2}$ ($0.32$ gm.) of ephedrine with belladonna during the day, 2 required gr. 1 ($0.65$ gm.) of pseudo-ephedrine with the belladonna and 2 only gr. $\frac{1}{2}$ ($0.32$ gm.) with the belladonna. One case improved with gr. $\frac{1}{2}$ ($0.32$ gm.) pseudo-ephedrine, but responded completely to gr. $\frac{1}{2}$ ($0.32$ gm.).

The treatment was given for from 1-4 months.

Brookfield found that months of persevering treatment were needed in certain cases before improvement occurred. Of his 17 males and 15 females, 4 of each sex failed to improve.

Browne and Ford-Smith expressed their results as a comparison with the total possible number of beds that could be wet. Consequently, their results express the number of nights wet, not the number of times that enuresis occurred. Their cases were wakened for urination two hours after going to sleep.
Stalker and Band measured the degree of improvement on a rough percentage scale.

First eliminating organic causes, such as infection of urine, mechanical obstruction to emptying the bladder with resultant retention, and neurological defect interfering with the function of the bladder, Kittredge and Brown gave the treatment for two weeks. Enuresis re-commenced in 11 cases. These authors state that the treatment must, probably, always be given for 3 weeks, and that nightly treatment for one month may be necessary before any improvement occurs. An increase above a dosage of gr. ⅔ (0.049 gm.) in cases of failure produced no additional benefit. These authors record one case, a man 23 years of age and incontinent since a child, who showed no recurrence during an observation period of four years after receiving gr. ⅔ (0.049 gm.) nightly for three weeks. A boy, aged 9, incontinent "practically every night," showed no enuresis during an observation period of three years following two courses of treatment of three weeks each. Two other illustrative cases, each with freedom of recurrence over six months, are those of a 17-year-old female, an enuretic since infancy, who received gr. ⅔ (0.049 gm.) for three weeks, and a 3½-year-old boy who was given the same dose for one month. Enuresis ceased, but he was given an additional course of the same dosage for three weeks.

Present Investigation.

An investigation of the value of ephedrine in persistent nocturnal enuresis has been undertaken at Hortham Colony on a total of 90 resident mental defectives of both sexes and from 2 to 27 years of age. Although Kittredge and Brown found, by the use of sugar-coated pills substituted for the ephedrine, that suggestion plays no, or little, part in the treatment, the use of low-grade mental defectives was believed to reduce the effect of suggestion to negligible proportions.

Staff Supervision.

Clearly, the number of times that a case is found to be wet is related to the number of times that the nurse examines the sheets. For instance, a patient may wet the bed two or three times before the bed is examined, with the consequent result that one wet bed instead of two or three is recorded. The records of wet beds show the minimum and not the maximum number of times that the individual has passed urine. A good nurse who knows the patient at night will often be able to prevent a wet bed occurring by awaking the patient and causing him to micturate at the most advantageous times.

Instructions to the night staff, their knowledge of the cases and changes in staff may, in consequence, influence the results of investigations of treatment.

Investigations.

In the following investigations fluids were not restricted, but the cases were encouraged to micturate before going to bed and were awakened during the night. These practices were adopted before and during the test periods.
Test 1.—Small Dose.
Cases: 30 males, 12 females, from 2 1/2 to 18 1/2 years of age; 38 idiots, 2 imbeciles, 2 feeble-minded.
Incontinence: All incontinent every night.
Staff: All cases nursed by same staff. Instructed to record number of times wet nightly.
Dose: Gr. 1/2 (.032 gm.) between 6 and 7 p.m. nightly for 4 weeks. Records for 3 weeks.

Test 2.—Medium Dose.
Cases: 17 males from 10 1/2 to 23 3/2 years of age; 11 idiots, 5 imbeciles, 1 feeble-minded.
Incontinence: Observation for 2 weeks before treatment.
Staff: One nurse, who knew all cases thoroughly, during test.
Dose: Gr. 1/4 (.097 gm.) at 5-6 p.m. nightly for 12 weeks.

Test 3.—Doses Varying from Low to High.
Cases: 11 females from 17 to 26 years of age; 1 idiot, 9 imbeciles, 1 feeble-minded.
Incontinence: Observed for 2 weeks before treatment and continued for 2 weeks after cessation of treatment.
Staff: Accustomed to the cases. Instructed to examine frequently.
Dose: Gr. 1/4 (.049 gm.) to gr. 1/2 (.146 gm.) nightly, from 6-7 p.m. for 16 weeks.

Test 4.—Test of Effect Early or Late in the Night.
Cases: 21 males, 12 females from 2 1/2 to 26 1/2 years of age. Twenty of these cases were not included in Tests 1, 2 and 3.
Incontinence: Not cured by ephedrine.
Staff: Instructed to examine cases before and after midnight.
Dose: Gr. 1/2 (.065 gm.) or 2 (.13 gm.) nightly for 8 to 11 nights.

Results.

Test 1.
During the test no alteration was made in the routine examination and raising of the patients. The results were recorded continuously during the first, second and third weeks of treatment in 21 males and 11 females, and during the first, third and fourth weeks in 9 males and 1 female.
The number of nights on which the cases were incontinent was, as compared with the period previous to treatment, reduced in 21 patients (50 per cent.) and stationary in 21 cases. Of the 30 males, 18 (60 per cent.) improved, but of the 12 females only 3 (25 per cent.) improved.
The number of times that each child was wet weekly decreased from the first week of treatment in 26 (61-9 per cent.) cases, remained stationary in 5 (7-1 per cent.) and became more numerous in 11 (26-2 per cent.).
Of the 30 males, 18 (60 per cent.) showed improvement, 4 (13 per cent.) remained stationary and 8 (27 per cent.) became worse. Of the 12 females, 8 (67 per cent.) improved, 1 (8 per cent.) showed no change and 3 (25 per cent.) deteriorated.

Only two patients, a feeble-minded boy, aged $6\frac{1}{2}$, and an idiot boy, aged $2\frac{1}{4}$, became completely continent during the three weeks of treatment. Two cases, an imbecile boy, aged $11\frac{3}{4}$, and a feeble-minded boy, aged $5\frac{1}{2}$, were completely continent for two of the three weeks.

Test 2.

In view of the failure of many cases to improve on the small dose given in Test 1, a test of three times the dose was carried out.

Although the nurse on duty throughout this test knew the patients well, no ephedrine was given for the first two weeks.

With regard to the number of times wet, 8 (47 per cent.) showed definite improvement, 3 (17-6 per cent.) showed doubtful improvement, 1 (5-9 per cent.) remained unchanged and 5 (29-4 per cent.) became worse. Only 2 cases became completely continent, both being so for one month of treatment. Of the 17 cases, 7 (41-2 per cent.) showed a decrease in the number of nights of incontinence, 2 (11-8 per cent.) showed a doubtful improvement, 7 (41-2 per cent.) showed no change and 1 (5-9 per cent.) became worse.

Six cases showed a marked temporary improvement, both with regard to the number of times incontinence occurred and to the number of nights on which incontinence took place. This temporary improvement persisted from 4 to 10 weeks after the commencement of the treatment. It occurred in cases who showed improvement at the end of the treatment, cases who remained stationary and those who had become worse by the end of the test period.

Test 3.

In this test no ephedrine was given for the first two weeks. During the third and fourth weeks gr. $\frac{1}{4}$ (0-049 gm.) was given. At the beginning of the fifth week the dose was decreased to gr. $\frac{1}{4}$ (0-032 gm.) in 5 cases and increased to gr. 1 (0-065 gm.) in 6 cases. The doses were maintained at these levels during the sixth week. At the commencement of the seventh week all doses were increased by gr. $\frac{1}{4}$ (0-016 gm.), and a similar increase was made at the beginning of the 9th, 11th, 13th and 15th weeks, a dosage of gr. 2 $\frac{1}{4}$ (1-146 gm.) being given to 6 cases during the 15th and 16th weeks. No treatment was given during the 17th and 18th weeks.

With regard to the number of nights on which wet beds occurred, 2 imbeciles showed no improvement on any of the doses given, these two reaching a dosage of gr. 2 $\frac{1}{4}$ (1-146 gm.). The remaining 9 cases improved, one for 12 weeks only and another for 8 weeks only, in spite of the continuance of the ephedrine. Seven cases (63-5 per cent.) maintained their improvement even during the final two-week period with no treatment.

The number of times that wet beds were found decreased in every case, although in the two imbeciles showing no improvement in the number of
nights wet, the reduction lasted for 12 and 14 weeks only. In a third case, an idiot, the improvement ceased after the cessation of the treatment. In the remaining 8 cases (one died earlier) the improvement persisted during the two weeks following the termination of the treatment, although the degree of improvement became less. No case became worse.

The increase of the dose, up to twice its initial strength, did not increase the improvement obtained with the initial smaller dose, either as regards the number of wet beds or the number of nights on which wet beds occurred.

Test 4.

In Tests 1, 2 and 3 the ephedrine was given in the evening between 5 p.m. and 7 p.m. It was thought that, possibly, in cases who failed to react satisfactorily, the incontinence might have occurred late in the night only. In consequence a second dose given after midnight might be of benefit.

The total of 33 cases gave 181 wet beds before midnight and 266 after midnight during the periods of observation, which were the equivalent of 322 nights for one patient. If the duration of the effect varied with the dose, then the cases receiving gr. 2 (13 gm.) should show a smaller proportion of wet beds after midnight than those receiving half this amount. Table II shows that this is not so. In fact, the ratio is greater in the cases receiving the higher dose.

**Table II.—Varying Dosage and Time of Enuresis.**

<table>
<thead>
<tr>
<th></th>
<th>gr. 1 (0.065 gm.)</th>
<th>gr. 2 (1.13 gm.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Dose</td>
<td>gr. 1 (0.065 gm.)</td>
<td>gr. 2 (1.13 gm.)</td>
</tr>
<tr>
<td>2. Wet beds before midnight</td>
<td>126</td>
<td>44</td>
</tr>
<tr>
<td>3. Wet beds after midnight</td>
<td>176</td>
<td>85</td>
</tr>
<tr>
<td>4.</td>
<td>After MN</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td>Before MN</td>
<td>2</td>
</tr>
</tbody>
</table>

When a comparison is made on the same patients, first receiving gr. 1 (0.065 gm.) and later gr. 2 (1.13 gm.), similar results are obtained. Table III shows a comparison on 8 cases extracted from Table II. The cases were given gr. 1 (0.065 gm.) for a period equivalent to 1 case over 48 nights and gr. 2 (1.13 gm.) equivalent to 1 case over 35 nights. The Table shows that the proportion of wet beds after midnight is higher with the larger dose.

**Table III.—Same Cases given first gr. 1 (0.065 gm.) and later gr. 2 (1.13 gm.).**

<table>
<thead>
<tr>
<th></th>
<th>gr. 1 (0.065 gm.)</th>
<th>gr. 2 (1.13 gm.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Dose</td>
<td>gr. 1 (0.065 gm.)</td>
<td>gr. 2 (1.13 gm.)</td>
</tr>
<tr>
<td>2. Wet beds before midnight</td>
<td>20</td>
<td>12</td>
</tr>
<tr>
<td>3. Wet beds after midnight</td>
<td>43</td>
<td>32</td>
</tr>
<tr>
<td>4.</td>
<td>2.15</td>
<td>2.67</td>
</tr>
</tbody>
</table>
The greater number of wet beds after midnight in Tables II and III could
be due to a disproportion in the hours before and after midnight during which
the night staff were on duty. The nurses were on duty for four hours before
midnight and eight hours after, the proportion of 1 to 2 resembling the ratio
between wet beds before midnight and wet beds after midnight.

Sheets.

In Test 2 a record was kept of the number of sheets wet and sent to the
laundry. A definite decrease occurred (Table IV).

\[ \text{Table IV.—Sheets Sent to Laundry.} \]

<table>
<thead>
<tr>
<th>Pre-treatment</th>
<th>1st.</th>
<th>2nd.</th>
<th>3rd.</th>
<th>4th.</th>
<th>5th.</th>
<th>6th.</th>
</tr>
</thead>
<tbody>
<tr>
<td>211</td>
<td>132</td>
<td>81</td>
<td>128</td>
<td>138</td>
<td>133</td>
<td>145</td>
</tr>
</tbody>
</table>

Temperature.

The frequency of micturition is commonly stated to be related to the atmo-
spheric temperature. As an alteration in temperature might have influenced
the results of the three tests, the nightly dormitory temperatures at midnight
and at 4 a.m. for the cases of Test 2 were averaged, the means for each fort-
nightly being shown in Table V. These means are the means of the mean mid-
night and 4 a.m. temperatures of each night and averaged for each fortnightly

\[ \text{Table V.—Total Wet Beds for Series of 17 Male Defectives.} \]

<table>
<thead>
<tr>
<th>Periods</th>
<th>1-6 = October to February; 7-12 = April to May; 13-17 = July to August.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean temp.</td>
<td>48.4 46.5 44.5 46.9 42.1 50 51.3 52.7 57.8 58.4 63.8 61.3 64.7</td>
</tr>
<tr>
<td>Number of nights wet</td>
<td>79 70 87 106 103+ 116+ 106 96 95 74 121 115 106 134</td>
</tr>
<tr>
<td>Number of times wet</td>
<td>84 82 122 138 128+ 142+ 145 142 142 118 154 141 144 178</td>
</tr>
</tbody>
</table>

+ = one patient excluded from series as in hospital.

The Table shows that when the higher dormitory temperatures
occurred not only did no reduction of wet beds take place, but an actual
increase was noted. The rise in dormitory temperature did not, therefore,
influence the test results favourably.

Mode of Action.

Parkhurst, and Kittredge and Brown, point out that ephedrine contracts
the trigone and relaxes the fundus of the bladder. The last two writers add
that it activates the internal sphincter, inhibits the detrusor muscle and con-
tracts the ureteral orifices.
TABLE XVIII.—Number of Cases in Which Improvement Persisted to End of Observation, with Duration of Improvement in Weeks.

<table>
<thead>
<tr>
<th>Duration in weeks</th>
<th>0-3+</th>
<th>4-6+</th>
<th>7-9+</th>
<th>10-12+</th>
<th>13-16+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nights wet</td>
<td>Test 2 max. imp.</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Test 3 max. imp.</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Test 2 total imp.</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>4</td>
<td>—</td>
</tr>
<tr>
<td>Test 3 total imp.</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Times wet</td>
<td>Test 2 max. imp.</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Test 3 max. imp.</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Test 2 total imp.</td>
<td>1</td>
<td>0</td>
<td>4</td>
<td>6</td>
<td>—</td>
</tr>
<tr>
<td>Test 3 total imp.</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>9</td>
</tr>
</tbody>
</table>

These tables show that improvement may not occur until the ephedrine has been given for from 9 to 11 weeks, although such a long delay is unusual. A delay of approximately a month before improvement occurred was common.

Ephedrine was given continuously to the cases of Test 3 for one year. After about 8–9 months of treatment the numbers of cases showing improvement decreased (Table XIX), the numbers of those becoming worse or showing no change increased. It may, therefore, be that ephedrine should be given intermittently, and that too great a length of dosage may reduce the earlier beneficial results.

TABLE XIX.—Continuous Treatment for One Year.

A = October to February; B = April to May; C = July to August.

<table>
<thead>
<tr>
<th>Periods</th>
<th>Nights wet</th>
<th>Times wet</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A.</td>
<td>B.</td>
</tr>
<tr>
<td>Improved</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Doubtful</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>No change</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Worse</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

CONCLUSION.

1. Ephedrine hydrochloride improved nocturnal enuresis in approximately 40–60 per cent. of mental defectives, but made some cases worse.
2. The improvement was of considerable duration in from 66 to 75 per cent. of cases.
3. An oral dose of approximately gr. 1 (0.065 gm.) was required nightly for children and adults. Higher doses did not produce greater improvements.
4. A rise in the dormitory temperature did not decrease the total number of wet beds.
5. The number of sheets sent to the laundry decreased.
6. Higher-grade cases reacted more favourably than did lower-grade defectives.
7. Older patients showed a higher improvement-rate than did the younger.
8. With adequate dosage, the degree of improvement in each case was usually from 80 to 100 per cent.
9. Although improvement persisted to the end of the observation periods (i.e. for 3 and 4 months) in about 75 per cent. of the cases, the maximum improvement persisted for this length of time in only 25 per cent. of the cases.

10. Improvement did not commence until approximately 3 months after the beginning of the treatment in one case. The majority of improvements commenced before the end of one month.

11. The numbers of cases maintaining their improvement when ephedrine was given continuously decreased after 8 or 9 months, so intermittent dosage, as for a month with monthly intervals, may be more advantageous.

In conclusion, my thanks are due not only to Dr. J. F. Lyons, Medical Superintendent of Hortham Colony, for permission to carry out these investigations, but also to Chief Male Nurse H. T. Hills and Sister E. M. Walker, who were responsible for the excellent keeping of the numerous records required.

REFERENCES.

Christopherson, J. B., and Broadbent, M. (1934), ibid., 1, 978.