Ability of Serotonin and Norepinephrine to Mimic the Central Effects of Reserpine on Vasomotor Activity

By J. W. McCubbin, M.D., Y. Kaneko, M.D., and Irvine H. Page, M.D.

Employing electroneurographic techniques, Bein and McCubbin and Page have shown that a significant portion of the acute cardiovascular effects of reserpine is mediated centrally. The mechanism involved is not known but, since serotonin has been shown to inhibit central synaptic transmission, Brodie et al. and Shore et al. have suggested that the sedative effect of reserpine might depend upon its ability to cause release of serotonin from its bound form within the brain to a free and active one. Release of norepinephrine from its bound form may also be involved, since Holzbauer and Vogt have shown that reserpine causes its release and Marrazzi and Hart have observed that it blocks cerebral synaptic transmission.

If the central effects of reserpine on vasomotor activity depend upon release of serotonin and norepinephrine, it should be possible to reproduce these effects by injecting the amines themselves directly into the cerebrospinal fluid, since reserpine is effective when given in this manner. It was our purpose to test this hypothesis. The precursors of serotonin and norepinephrine, 5-hydroxytryptophan (5-HTP) and 3,4-dihydroxyphenylalanine (DOPA), respectively, were used in the majority of experiments.

Methods

Adult mongrel dogs, weighing between 9 and 16 Kg., were anesthetized with morphine (2 mg./Kg. s.c.) and sodium pentobarbital (15 mg./Kg. i.v.). The vagus-sympathetic-depressor trunks were cut in all experiments on anesthetized dogs, loose ties were placed about both common carotid arteries, and intermittent positive pressure respiration was employed. Main arterial pressure was recorded on a smoked drum by a mercury manometer connected to a cannulated femoral artery. Heart rate was recorded on the same drum by interrupting the vertical sweep of the writing arm of a Palmer drop recorder with the animal's amplified electrocardiogram. The central cut end of a sciatic nerve and of a vagus nerve were stimulated with a square wave of 1 to 10 ms. duration, at from 20 to 30 e.p.s., at from 1 to 10 volts and for from 15 to 30 seconds.

Either a few days or a few hours before experiments on 53 dogs, a cannula was implanted into a lateral ventricle using the method described by Feldberg and Sherwood. In 21 dogs, a needle or cannula was inserted into the cisterna magna at the time of the experiment. Drugs injected centrally were dissolved in 0.2 to 0.5 ml. of physiologic saline, usually adjusted to pH 7.0. There was no close correlation between dosage and body weight; hence, total dosage (rather than mg./Kg.) is given in the results.

To measure pressor responsiveness, norepinephrine, or levarterenol (5 μg.) and serotonin creatinine sulfate (60 μg. of base) were injected intravenously.

In order to measure afferent electric activity of the carotid sinus nerve, the cut peripheral end of the nerve was placed on silver or platinum electrodes connected to conventional capacity-coupled amplifiers and nerve activity, photographed on the face of a cathode ray tube simultaneously with arterial pressure measured with the aid of a strain gage manometer. Drying of the nerve was prevented by humidification of the surrounding air and by immersing it in a pool of mineral oil; this made it possible to record for as long as several hours without change in electric activity due to deterioration of the preparation. Recordings were also made from small bundles teased from the whole nerve.

Experiments were performed on 6 unanesthetized dogs after inserting a cannula into a lateral ventricle approximately one week beforehand. Approximately one month beforehand, one carotid sinus nerve was sectioned and both aortic depressor nerves were cut at the level of the carotid sinus. Section of the aortic depressor nerves was facilit
Table 1

<table>
<thead>
<tr>
<th>Drug</th>
<th>Condition of dog</th>
<th>No. of dogs</th>
<th>Dosage (average and range) mg.</th>
<th>Change in mean arterial pressure (Control Change before and after mm. Hg)</th>
<th>Change in carotid occlusion response before and after mm. Hg</th>
<th>Reduction %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reserpine</td>
<td>Anesthetized</td>
<td>10</td>
<td>1.5 (0.5 - 2.5)</td>
<td>133 -23 114 51 55</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unanesthetized</td>
<td>2</td>
<td>1.5 (1 - 2)</td>
<td>160 -19 107 43 60</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pretreated with</td>
<td>3</td>
<td>1.5 (0.5 - 2.5)</td>
<td>128 -25 97 13 87</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>JB 516,*</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>5-HTP</td>
<td>Anesthetized</td>
<td>20</td>
<td>2.1 (0.25 - 5)</td>
<td>134 -32 108 35 68</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unanesthetized</td>
<td>4</td>
<td>4.0 (2 - 5)</td>
<td>158 -41 92 31 60</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pretreated with</td>
<td>6</td>
<td>1.3 (0.25 - 2)</td>
<td>142 -33 118 17 86</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>JB 516,*</td>
<td></td>
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</tr>
<tr>
<td>DOPA</td>
<td>Anesthetized</td>
<td>12</td>
<td>2.6 (0.5 - 10)</td>
<td>137 -26 108 54 50</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Pretreated with</td>
<td>6</td>
<td>4.7 (0.5 - 10)</td>
<td>130 -28 106 24 77</td>
<td></td>
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<tr>
<td></td>
<td>JB 516,*</td>
<td></td>
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</tr>
<tr>
<td>Serotonin</td>
<td>Anesthetized</td>
<td>6</td>
<td>5.0 (1 - 10)</td>
<td>132 -28 105 35 60</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pretreated with</td>
<td>2</td>
<td>5.0 (5)</td>
<td>136 -32 123 20 84</td>
<td></td>
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<tr>
<td></td>
<td>JB 516,*</td>
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<td></td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>Anesthetized</td>
<td>5</td>
<td>0.22 (0.05 - 0.5)</td>
<td>135 -28 107 49 54</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*5 or 10 mg. of JB 516 (beta-phenylisopropylhydrazine) were injected into a lateral ventricle or the cisterna magna more than 90 minutes beforehand.

Results

**Effect of Central Administration of Reserpine in Anesthetized Dogs**

In order that the central effects of 5-HTP, DOPA, serotonin and norepinephrine might be compared accurately with the acute central, rather than peripheral, action of reserpine, reserpine was injected into a lateral ventricle or into the cisterna magna of 10 anesthetized dogs in total dosage of from 0.1 to 2.5 mg. The smaller dose was without effect; 0.5 mg., or more, caused lowering of arterial pressure of from 11 to 52 mm. Hg (average 23 mm. Hg, table 1) and these hypotensive responses were usually accompanied by bradycardia though the vagus nerve had been cut. Response to occlusion of the common carotid arteries was inhibited by from 31 to 77 per cent (average 55 per cent). There was slight augmentation, or no change, in response to norepinephrine given intravenously and that to serotonin was essentially unchanged. Reserpine's inhibitory activity appeared within 30 minutes, was maximum after approximately one hour, and persisted for the several hours of the duration of the experiments.

When reserpine was given intravenously, 2 mg./Kg., or more, were required to produce cardiovascular responses comparable to those produced by a total dose of 1 mg. given centrally. The initial, moderately prolonged pressor response that follows intravenous injection of reserpine usually did not appear following central administration, and the...
small total dose of reserpine given centrally was without effect on either arterial pressure or the carotid occlusion response when given intravenously.

In contrast with the effect on response to carotid occlusion, reflex pressor responses to stimulation of a cut central end of a vagus or sciatic nerve were only moderately depressed or little changed after central injection of 1 or 2 mg. of reserpine.

Central Effect of 5-Hydroxytryptophan in Anesthetized Dogs

Hydroxytryptophan was injected into a lateral ventricle of 15 dogs and into the cisterna magna of 5 dogs in total dosage ranging from 0.1 to 5.0 mg. It caused moderate to marked lowering of arterial pressure (15 to 77 mm Hg; average 32) lasting for from 1 to 2 or more hours and the degree and duration of the hypotensive response correlated roughly with dosage. The minimum effective dose was from 0.25 to 0.5 mg. when given into a lateral ventricle and 1.0 mg. when given into the cisterna magna. Despite prior section of the vagus nerves, hypotensive responses were usually accompanied by bradycardia.

Responses to carotid occlusion were depressed by from 35 to 96 per cent (average 68 per cent) depending on dosage (table 1, fig. 1). This blocking action appeared within 10 minutes (appreciably less time than was required for the effect of reserpine to appear), increased gradually to reach a maximum within from 30 to 60 minutes, and persisted to some degree during an additional 1 to 2 hours of observation. Response to norepinephrine given intravenously was slightly augmented or unchanged. When 5-HTP was reinjected after recovery from the initial dose, the effects were less pronounced and often markedly so.

Inhibition of the carotid occlusion response was usually accompanied by decrease in resting arterial pressure, but was not attributable to it since inhibition persisted when arterial pressure was elevated to, or above, the previous control level by intravenous infusion or injection of renin. It is unlikely that continued inhibition of the carotid occlusion response during the pressor response to renin depended on a direct local effect of angiotensin on the carotid sinus wall, since we have shown previously that relatively enormous dosage of angiotensin injected into the adventitia of the carotid sinus, or directly into the lumen of a "tight" sinus, has slight, or no, effect on the occlusion response. There is currently no published evidence that pressor concentrations of circulating vasoconstrictor drugs modify baroreceptor sensitivity. Epinephrine (10⁻⁶) has been found by Neil not to influence baroreceptor sensitivity in the perfused sinus. Additionally, there was poor correlation between degree of inhibition of the occlusion response and severity of the hypotensive response; in some experiments there was a very slight fall in arterial pressure but pronounced inhibition of the occlusion response.

Like reserpine, 5-HTP was less effective in inhibiting the pressor response to stimulation of the cut central end of a vagus or sciatic nerve than that to carotid occlusion. From 2 to 5 mg., injected centrally, decreased the
response moderately in some experiments but had no effect in others, while markedly inhibiting the response to carotid occlusion. Figure 1 illustrates this somewhat selective action.

Bogdanski, Weissbach and Udenfriend suggested that 5-HTP, given intravenously, might produce its blocking effect on the carotid occlusion reflex by an action on baroceptors. While it seemed unlikely that sufficient of the small amount of 5-HTP given centrally in the present experiments could escape to produce this hypothetical effect, afferent electric activity of one carotid sinus nerve was measured before and after intraventricular injection of 5 mg. of 5-HTP in each of 2 dogs. Fall in arterial pressure was equal to that in the previous group of experiments and there was marked inhibition of the response to carotid occlusion (elicited by compression of the common carotid artery supplying the opposite innervated sinus, the vagus-sympathetic-depressor trunks having been cut). If these effects depended upon a direct action of 5-HTP on baroceptors—in the manner of norepinephrine or other vasoconstrictor drug applied locally—there would have been marked increase in electric activity. Instead, nerve activity diminished (fig. 2) as arterial pressure declined, indicating that increased baroceptor stimulation did not account for the hypotension and blockade of the occlusion response. During the hypotensive response, nerve activity showed a marked increase during pressor responses to intravenous injection of norepinephrine, indicating that baroceptors were still capable of responding to stimulus. Similar results were obtained with few-fiber preparations (fig. 2).

In 2 other experiments, the same dosage of 5-HTP as was employed by Bogdanski et al. (60 mg./Kg.) was given intravenously during measurement of carotid sinus nerve activity. There was an initial pressor response lasting several minutes, during which nerve activity was increased; following this, there was progressive decline in arterial pressure and complete blockade of the carotid occlusion response. Nerve activity again decreased as the pressure declined and again showed marked increase during pressor responses to intravenous injection of norepinephrine (fig. 3).

These results thus do not confirm the suggestion that 5-HTP causes hypotension and blockade of the carotid occlusion response by a direct effect on carotid sinus baroceptors.

Central Effect of 3,4-Dihydroxyphenylalanine in Anesthetized Dogs

Qualitatively, response to DOPA was the same as to 5-HTP; it was slightly less active on a weight basis and, like 5-HTP, was more effective when given into a lateral ventricle than when given into the cisterna magna. From 0.5 to 10 mg. of DOPA caused bradycardia and an average decline of 26 mm. Hg in arterial pressure that lasted for more than one hour in 12 dogs. The carotid occlusion response was depressed by from 27 to 72 per
cent (average 50 per cent; table 1). Some inhibition appeared within from 15 to 30 minutes and it reached a maximum within one hour. The duration of the effect was shorter than that of 5-HTP; when small dosage was employed, recovery was complete within 2 hours. As with 5-HTP, a second dose of DOPA had a less pronounced effect, and it also was less active against the pressor response to stimulation of the cut central end of a sciatic or vagus nerve than that to carotid occlusion.

Central Effect of Serotonin in Anesthetized Dogs

Serotonin had the same effect on arterial pressure, heart rate and the carotid occlusion response as did 5-HTP, but the minimum effective dose was 1 or 2 mg., compared with 0.5 mg. for 5-HTP. In 8 dogs, from 1 to 10 mg., injected into a lateral ventricle or the cisterna magna, caused an average decline of 28 mm. Hg in arterial pressure and reduced the response to carotid occlusion by an average of 66 per cent (table 1).

Central Effect of Norepinephrine in Anesthetized Dogs

Norepinephrine had the same effect as did DOPA but, unexpectedly, was as, or more, active on a weight basis. The minimum effective dose was from 50 to 100 μg. compared with approximately 1 mg. for DOPA. Fifty to 500 μg. reduced arterial pressure by an average of 28 mm. Hg and the carotid occlusion response by an average of 54 per cent in 5 dogs (table 1). The blocking action appeared within 20 minutes and reached its maximum within one hour (fig. 4).

Central Effect of Various Other Amino Acids in Anesthetized Dogs

In control experiments, 5 mg. of l-leucine, l-proline, dl-serine, l-valine or l-arginine were injected separately into a lateral ventricle of each of 4 dogs. These agents had no significant effect on arterial pressure or the response to carotid occlusion during the same periods of observation as in the preceding experiments. Since serotonin had been used in the form of the creatinine sulfate salt, 5 mg. of creatinine were also injected into a lateral ven-

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Figure 3

Top trace each strip: intrasinus pressure; bottom trace: activity carotid sinus nerve. Breaks in top reference line at 1-second intervals. Description in text.
Figure 4
Effect of norepinephrine given into lateral ventricle of anesthetized dog. Time marks: 1 minute.

Effect of norepinephrine given into lateral ventricle or the cisterna magna of 17 anesthetized dogs. It usually produced a rise in arterial pressure that averaged 29 mm. Hg and, during this rise, the carotid occlusion response was inhibited by an average of 52 per cent. Both arterial pressure and the occlusion response returned to control values within from 30 to 90 minutes; with recovery, the central effects of the following agents were measured (table 1):

1. 5-HTP
Small doses (0.25 to 2.0 mg.) had more marked and longer lasting effects than in dogs not pretreated with JB 516. In 6 anesthetized dogs, the carotid occlusion reflex was reduced by an average of 86 per cent and there was marked inhibition of the pressor response to stimulation of the cut central end of a sciatic nerve.

2. Serotonin
Central inhibitory activity was augmented like that of 5-HTP. In 2 dogs, the carotid occlusion response was reduced by 89 and 79 per cent.

3. DOPA
Central action was augmented in 6 dogs, in which it was tested. The carotid occlusion was reduced by an average of 77 per cent. Intraventricular administration of 0.5 mg., which had little, or no, effect in dogs not pretreated with JB 516, caused marked blockade of the occlusion response.

4. Dopamine
This agent, when injected centrally in doses of from 0.2 to 1.0 mg., caused little, or no, change in arterial pressure or the response to carotid occlusion in dogs not pretreated with JB 516. After pretreatment, the same dosage caused lowering of arterial pressure and marked inhibition of the carotid occlusion reflex.

5. Reserpine
The central action of reserpine was augmented markedly by pretreatment with JB 516. Injection of 1.5 mg. inhibited the response to carotid occlusion by an average of 87 per cent and there was also marked inhibition of the pressor response to stimulation of the cut central end of a sciatic or vagus nerve (fig. 6).

Discussion
These experiments demonstrate that serotonin and norepinephrine and their respective precursors, 5-HTP and DOPA, mimic the centrally mediated effects of reserpine when they are injected into a lateral ventricle of anesthetized or unanesthetized dogs. The effects consisted of decrease in arterial pressure, marked inhibition of the carotid occlusion response and bradycardia. In the group of anesthetized dogs, bradycardia usually occurred despite prior section of the vagus nerves, due apparently to reduction of tonic sympathetic chronotropic activity.

Since reserpine is known to cause release of serotonin and norepinephrine from their bound forms in the brain, it is plausible that its central cardiovascular effects may be mediated by these amines; the experiments reported here are all consistent with this hypothesis, but of course, do not prove it. The manner in which serotonin and norepinephrine locally modify vasomotor activity is not known, but both agents have been demonstrated by Marrazzi and Hart and by Slocombe, Hoag...
SEROTONIN, NOREPINEPHRINE AND RESERPINE

land and Tozian to inhibit central synaptic transmission.

Qualitatively, responses to centrally administered reserpine, DOPA, 5-HTP, norepinephrine and serotonin were the same, and they were specific in that other amino acids (leucine, proline, serine, valine and arginine) were without effect in control experiments. As would be expected, an amine oxidase inhibitor augmented the central action of the active amines and it augmented the central action of reserpine as well, implying again that the central cardiovascular effects of reserpine may be due to release of amines from a bound to an active form.

Since serotonin and norepinephrine elicited the same cardiovascular effects when injected centrally, they probably act on the same receptors, or upon different receptors but ones that mediate the same function. This is not surprising since, phylogenetically, serotonin seems to be the neurohumor of primitive organisms to be displaced, at least in part, by norepinephrine in more highly developed organisms. Both substances are concentrated in the limbic system and hypothalamic areas which, in turn, are closely associated with central vasomotor activity. There is the strong implication, then, that both amines play a role in the physiologic regulation of vasomotor discharge, and that the acute effects of therapeutic doses of reserpine may depend upon modification of this regulatory function.

Employing electronphrenographic technics, we have shown previously that a large portion of the acute cardiovascular effects of reserpine given systemically is mediated centrally. The present experiments support this view, since one twentieth of the usual intravenous dose of reserpine given centrally produced equivalent cardiovascular effects; this small dose of reserpine given intravenously was without detectable effect.

The relative preferential inhibition of the carotid occlusion response by both reserpine and the active amines, when compared with inhibition of the reflex pressor response to stimulation of a cut central end of a sciatic or vagus nerve, is in accord with the observation of Bogdanski et al., who found that much larger doses (60 mg./Kg.) of 5-HTP given intravenously had the same selective action. They suggested that inhibition of the carotid occlusion response might be due to a local effect on baroceptors. It was found in the present experiments that 5-HTP, whether given into a lateral ventricle in small dosage or intravenously in the larger dosage employed by Bogdanski et al., caused decrease of afferent electric activity in the carotid sinus nerve during the period of hypotension and blockade of the carotid occlusion response. Had the cardiovascular effects been due to a direct action of 5-HTP on baroceptors, there would have been an increase in activity such as follows local application of norepinephrine to the carotid sinus. Thus, the effect of 5-HTP appears to be mediated centrally rather than through the more peripheral carotid sinus baroceptor mechanism. That baroceptors were able still to respond to stimulation during the effect of 5-HTP is indicated by the marked increase in nerve activity that accompanied pressor responses to intravenous injections of norepinephrine.

We have previously enumerated the various actions of serotonin that determine the often unpredictable, amphibaric arterial pressure response to its intravenous injection. It is appropriate to add here that the usual depressor response to intravenous infusion of serotonin in dogs may depend in part upon...
Figure 6
Effect of combined injection of an amine oxidase inhibitor and reserpine into lateral ventricle of anesthetized dog after 2 hours. V: stimulation central end vagus nerve; Sc: stimulation central end of sciatic nerve; CO: carotid occlusion response. Time marks: 1 minute.

its central inhibitory activity, assuming that sufficient amount of the drug penetrates the blood-brain barrier. The question of permeability of the blood-brain barrier to serotonin is unsettled. Udenfriend, Weissbach and Bogdanski\textsuperscript{18} found no detectable increase of serotonin in brain tissue of dogs given 60 mg./Kg. peripherally. Shore et al.\textsuperscript{5} reported a slight increase of serotonin in brain tissue of mice when 100 mg./Kg. were given parenterally. McLsaac and Page\textsuperscript{19} were able to demonstrate radioactivity in brain tissue of rats and rabbits after parenteral injection of radioactive serotonin; this strongly suggests penetration of the blood-brain barrier but does not prove it, since metabolic products of serotonin may have accounted for the radioactivity detected. The best evidence currently available that serotonin does penetrate the blood-brain barrier are the demonstrations that serotonin given into the blood stream exerts measurable effects that are mediated by the brain; 5-HTP has been shown to penetrate more readily than serotonin.\textsuperscript{18}

Other experiments suggesting that serotonin and norepinephrine readily may penetrate the blood-brain barrier are those of Taylor and Page,\textsuperscript{20} in which it was shown that norepinephrine injected into the carotid artery of a perfused dog's head caused a neurogenically mediated fall of systemic pressure that was independent of the carotid sinus buffer mechanism. Centrally induced hypotensive responses by norepinephrine in these experiments may have depended upon the same mechanism as the one involved in the present experiments. Additionally, Bhargava and Borison\textsuperscript{21} have shown in cats that the intravenous administration of serotonin, like reserpine, caused depression of the pressor response to medullary stimulation while not affecting the pressor response to spinal stimulation.

Summary
Reserpine, serotonin, norepinephrine, 5-hydroxytryptophan and 3,4-dihydroxyphenylalanine had qualitatively the same cardiovascular effects when they were injected into a lateral ventricle or into the cisterna magna. All lowered arterial pressure, usually caused bradycardia despite prior section of the vagus nerves, and caused marked inhibition of the pressor response to occlusion of the common carotid arteries. Essentially the same results were obtained in unanesthetized as in anesthetized dogs. On a weight basis, norepinephrine was the more active amine tested and 5-hydroxytryptophan was more active than serotonin and 3,4 dihydroxyphenylalanine. Reserpine injected centrally had an effect
equivalent to that of 20 or more times larger dosage given intravenously. All drugs were more active against the response to carotid occlusion than against the reflex pressor response to stimulation of a cut central end of a sciatic or vagus nerve. Decreased afferent electric activity of the carotid sinus nerve accompanied lowering of arterial pressure following central injection of small dosage, or intravenous injection of large dosage, of 5-hydroxytryptophan, indicating that the cardiovascular effects are not due to a direct action of 5-hydroxytryptophan on carotid sinus baroreceptors.

Central injection of an amine oxidase inhibitor, beta-phenylisopropylhydrazine, markedly augmented and prolonged the cardiovascular effects of the amines and of reserpine as well.

These results are all consistent with, though they do not validate, the premise that the acute cardiovascular effects of reserpine are mediated centrally by serotonin and/or norepinephrine, either released from a bound and inactive to a free and active form, or formed by decarboxylation of their respective amino acids.

**References**

12. Bodanski, D. F., Weissbach, H., and Udenfriend, S.: Pharmacological studies with the...


15. PAGE, I. H.: Serotonin (5-hydroxytryptamine); the last four years. Physiol. Rev. 38: 277, 1958.


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