Integration of the cardiovagal mechanism in the medulla oblongata of the cat

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The central cardiovagal mechanism of the medulla oblongata was explored by stimulation and ablation techniques in the anesthetized cat. Insertion of an electrode into the nucleus solitarius (NS) occasionally evoked slight and transient bradycardia, but similar mechanical irritation to the nucleus ambiguus (NA) usually evoked prolonged and intense bradycardia. Electrical stimulation of the dorsal motor nucleus of the vagus (DNV) produced no or little bradycardia. Stimulation of NS and NA consistently produced cardiac slowing with a latency of less than 2 s and the effect was more prominent in the NA. Contralateral vagotomy did not significantly affect the bradycardia on the NS and NA stimulation but ipsilateral vagotomy caused a complete abolition. Lesions of the NA or DNV largely or completely abolished the bradycardia consequent to NS stimulation. Extensive destruction of the NS and/or DNV did not affect the bradycardia resulting from NA stimulation. Destruction of the ventral midline area partially reduced the bradycardia on NS stimulation by 36–54%. The results suggest that the sequence of the three vagal nuclei for cardiac inhibition runs in the following order: NS, DNV, and NA. Synaptic connections are probably scanty in the DNV. Part of the vagal pathway passes through the ventral midline area before it reaches the NA. A scheme of the neural pathway for reflex bradycardia of vagal origin has been proposed.

THE BASIC CARDIOVASCULAR FUNCTIONS are integrated in the medulla oblongata (6, 7, 19, 25, 28). The nature of the receptors, effectors, and afferent as well as efferent limbs of the cardiovascular reflexes have been relatively well documented (10, 13). Yet, little is known regarding the precise localization, pathways, and functions of the integrating mechanism in the medulla. The sympathetic component of the reflex, i.e., vasomotor, cardiocacceleratory, and augmentor responses, has been found dependent on the integrity of the midline area, the dorsal ventricular grey, or the dorsal reticular formation (6). Opinions on the vagal component of the cardioinhibitory functions are still debatable (3, 12, 17, 27), although it has been shown that vagal bradycardia elicited by baroreceptor and Bezold-Jarisch (chemoreceptor) reflexes requires the integrity of the nucleus solitarius (NS), the dorsal motor nucleus of the vagus (DNV), and the nucleus ambiguus (NA) (19).

Laborde (18) in 1888 first described cardiac slowing in dogs and cats with puncture stimulation to the NA region. This observation led him to believe that cardioinhibitory neurons were located in this nucleus. However, the concept was contested by Miller and Bowman (20) in 1916. They observed bradycardia in dogs by stimulating the floor of the fourth ventricle overlying the area of the DNV and concluded that the cardioinhibitory center was situated there. Thereafter, the DNV has generally been considered to be the source of vagal efferents to the heart (21).

Recent findings obtained by more precise stereotaxic and stimulation techniques (12, 27) have shown that electrical stimulation of the DNV elicited bradycardia occasionally in dogs and rarely in cats. On the other hand, stimulation of the NA regularly evoked prominent vagal cardiac inhibition in both species. Further, destruction of the DNV did not abolish the bradycardia resulting from brain stem ischemia (2). All the evidence suggests that DNV may not possess important cardio-inhibitory function.

In view of the inconsistencies, the present investigation was designed, by using stimulation and ablation techniques, to determine the sequence of the vagal nuclei involved in the central cardioinhibitory mechanism. It was also an attempt to elucidate the central pathways that mediate the reflex bradycardia of vagal origin.

METHODS

A total of 57 cats of either sex, weighing between 2–3.5 kg, was used. The animals were anesthetized intraperitoneally with a mixture of chloralose 40 mg/kg and urethan 400 mg/kg. Rectal temperature was maintained at 38°C throughout the course of the experiment. The trachea was intubated and the animal artificially ventilated with a Palmer respirator. Both cervical vagus nerves were dissected free for subsequent vagotomy as needed. Arterial pressure from the cannulated femoral artery was monitored with a Statham P23AC transducer, and the heart rate with a Grass 5P4 tachometer triggered by arterial pulses. All recordings were made on a Grass 5E polygraph.

The animal was placed in a prone position with the head fixed in a David Kopf stereotaxic instrument.
After removal of part of the occipital bone and the atlanto-occipital membrane, the floor of the fourth ventricle was exposed by elevating the posterior pole of the cerebellum with a spatula. The exposed surface was protected with a layer of mineral oil.

The sequence of cardiovagal pathways among the NS, DNV, and NA was determined by the following principle. Destruction of the nucleus near the afferent limb will not affect the bradycardia on stimulation of the nucleus distal to it. Ablation of the nucleus near the efferent side will block the bradycardia from stimulation of the proximal nucleus. The following observations have been made: 1) Effects of NS and/or DNV destruction on the bradycardia by NA stimulation. 2) Effects of NA lesions on the NS bradycardia. 3) Effects of DNV lesion on the NS or NA bradycardia. All these effects were observed after contralateral vagotomy to eliminate the possibility of fibers crossing to the other side. Because the three vagal nuclei are elongated, if a single discrete lesion did not produce a blockade, an extensive lesion was made in the nucleus. Extensive destruction of NA or DNV was accomplished by gentle suction through a fine capillary pipette connected to a vacuum, as described previously (6). Discrete lesions in the above nuclei and/or NA were made by electrolysis, i.e., by passing an anodal direct current of 2 mA for 25–35 s.

Stimulation of the medulla, in an area 1–3 mm rostral to the obex, was accomplished by a coaxial electrode (Hytemco wire, Precision Tube Co., 0.6 mm OD). This was kept at a 36–40° angle to the horizontal axis of the stereotaxic instrument in order to introduce the electrode almost vertically to the surface of the medulla. In some animals, two electrodes, with their tips 2.7–3.3 mm apart, were mounted side by side mostly on the same coronal plane, sometimes on the same sagittal plane, in order to reach the NS and NA simultaneously. The electrode was first inserted into the base of the brain and then was raised 0.2 mm successively until electrical stimulation elicited marked bradycardia. Thereafter, it was fixed in this position throughout the course of the experiment. Stimulation was provided by a Grass S4 square-wave generator coupled to an isolation unit. The parameters were 40–50 Hz, 0.5 ms, and 4–10 V. At the end of the experiment, the brain of the animal was perfused with saline, followed by 10% Formalin saline, and fixed in the latter solution for 7 days. The areas of stimulation and lesion were verified by frozen section and stained with Weil stain.

RESULTS

The cardiac slowing on stimulation of the NS, DNV, or NA and their changes after vagotomy or after selective destruction of the other two nuclei are summarized and explained as follows.

Heart Rate Changes on DNV, NS, and NA Stimulation and Effects of Vagotomy

In six animals, stimulation of the DNV on either side (3 right, 3 left) with intensity sufficient to evoke marked bradycardia when delivered to NS or NA did not produce any discernible slowing. Slight decrease of heart rate, 24 beats/min, was observed only when the intensity of the rectangular pulse was increased from 5–6 V to more than 10 V and the duration from 0.5 ms to 2 ms. Moreover, the bradycardia often appeared after a relatively long latency (5–9 sec).

In six other animals, insertion of the electrode into the NS alone (3 right, 3 left) occasionally produced transient and mild bradycardia. Subsequent electrical stimulation of the nucleus elicited cardiac slowing, 80–124 beats/min. In three of the six animals contralateral vagotomy (1 right, 2 left) was performed first. This procedure (1 right, 1 left) did not affect the bradycardia in two animals, but slightly reduced the bradycardia of the remaining one by 6%. The bradycardia was subsequently abolished by ipsilateral vagotomy. In the other three animals the bradycardia was abolished by ipsilateral vagotomy.

In 10 animals a single introduction of the electrode at or near the region of the NA, with the electrode remaining undisturbed, produced prolonged and intense bradycardia. The heart rate decreased from the resting level of 218 beats/min to 107 beats/min for as long as 25–65 min. In three of these animals ipsilateral vagotomy immediately terminated the bradycardia. In two animals, contralateral vagotomy only slightly reduced the bradycardiac action (less than 25 beats/min) for a short period of time (less than 15 s) and the heart rate soon returned to its previous level. Ipsilateral vagotomy subsequently terminated the bradycardia. In the remaining animals, after the prolonged cardiac slowing induced by mechanical irritation was over, electrical stimulation of the NA caused an immediate and profound bradycardia, 98–136 beats/min. Similarly, the bradycardia was not significantly affected by contralateral vagotomy, but was abolished by ipsilateral vagotomy. The above observation thus suggests that few crossed cardiovagal fibers exist and their actions are not significant.

Effects of NS and/or DNV Destruction on NA Stimulation

Table 1 summarizes the results of heart rate changes on stimulation of the NA before and after complete destruction of the NS and DNV in 11 animals. It can be seen that destruction of NS and/or DNV from the obex to the rostral medulla did not affect the bradycardia induced by stimulation of NA. Figure 1 depicts a typical example of this effect. In all 11 animals, contralateral vagotomy did not much affect the bradycardia on NA stimulation. Abolition of bradycardia was seen only after ipsilateral vagotomy.

Effects of DNV Destruction on NS or NA Stimulation

Table 2 summarizes the results of DNV lesion on the bradycardia induced by NS or NA stimulation in eight animals. Destruction of the DNV, extending from the obex to the rostral medulla, largely or completely eliminated the bradycardia on NS stimulation, but did not affect the NA-induced bradycardia. Figure 2 shows a
TABLE 1. Effects of destruction of nucleus solitarius and/or dorsal motor nucleus of vagus on bradycardia upon stimulation of nucleus ambiguus

<table>
<thead>
<tr>
<th>Cat No.</th>
<th>Lesion</th>
<th>Heart Rate, beats/min</th>
<th>Stimulation before lesion</th>
<th>Stimulation after lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td>302*</td>
<td>NS + DNV</td>
<td>228 - 92 (-136)</td>
<td>228 - 94 (-134)</td>
<td></td>
</tr>
<tr>
<td>118</td>
<td>NS + DNV</td>
<td>240 - 108 (-132)</td>
<td>238 - 110 (-128)</td>
<td></td>
</tr>
<tr>
<td>318</td>
<td>NS + DNV</td>
<td>226 - 94 (-132)</td>
<td>230 - 94 (-136)</td>
<td></td>
</tr>
<tr>
<td>325</td>
<td>NS + DNV</td>
<td>210 - 88 (-122)</td>
<td>220 - 86 (-134)</td>
<td></td>
</tr>
<tr>
<td>420</td>
<td>NS + DNV</td>
<td>224 - 120 (-104)</td>
<td>220 - 128 (-92)</td>
<td></td>
</tr>
<tr>
<td>226</td>
<td>DNV</td>
<td>196 - 94 (-102)</td>
<td>204 - 94 (-110)</td>
<td></td>
</tr>
<tr>
<td>326</td>
<td>DNV</td>
<td>224 - 102 (-122)</td>
<td>220 - 100 (-120)</td>
<td></td>
</tr>
<tr>
<td>501</td>
<td>DNV</td>
<td>190 - 104 (-86)</td>
<td>196 - 110 (-88)</td>
<td></td>
</tr>
<tr>
<td>228</td>
<td>DNV</td>
<td>212 - 88 (-134)</td>
<td>220 - 88 (-132)</td>
<td></td>
</tr>
<tr>
<td>523</td>
<td>DNV</td>
<td>240 - 94 (-146)</td>
<td>234 - 94 (-140)</td>
<td></td>
</tr>
<tr>
<td>606</td>
<td>DNV</td>
<td>244 - 120 (-124)</td>
<td>244 - 120 (-124)</td>
<td></td>
</tr>
</tbody>
</table>

Values are resting heart rate – maximum change of heart rate during stimulation. Numbers in parentheses are the extent of cardiac response. +, Increase. –, Decrease. * Tracings of this cat are shown on Fig. 1.

Effects of destruction of nucleus solitarius and/or dorsal motor nucleus of vagus on bradycardia upon stimulation of nucleus ambiguus

In the first seven animals in Table 3 two electrodes were simultaneously introduced into the NS and NA, side by side in the same sagittal plane. Stimulation of NS and NA produced cardiac slowing, 84 and 165 beats/min, respectively, and the action was not affected by contralateral vagotomy. After a lesion was made in the DNV, the cardiac slowing by NS stimulation disappeared, but that by NA stimulation remained unaltered until ipsilateral vagotomy was done. Data in which the DNV lesion involved the NS were discarded.

Effects of NA Lesion on NS Stimulation

In the first seven animals in Table 3 two electrodes were simultaneously introduced into the NS and NA. Stimulation of either nucleus evoked bradycardia. After a discrete electrolytic lesion was made on the NA, the bradycardia elicited by NS stimulation was largely or completely eliminated in spite of increases in the intensity of stimulation. Figure 3 shows a typical example of the effect on cat 114. In the remaining three cats, one

FIG. 1. Effect of extensive lesion of DNV and NS on bradycardia elicited by NA stimulation. Note stimulation of NA evoked marked bradycardia that was not affected by contralateral vagotomy or DNV and NS lesions until ipsilateral vagotomy was done. Photomicrograph illustrates tip of stimulation electrode on NA (arrow) and destruction of DNV and NS (extending from obex to rostral medulla).
Electrode was placed in the NS, whereas the other was 0.8 mm (304), 1.2 mm (210) and 2 mm (111) ventral to the NA. In all these cases stimulation elicited little or no bradycardia. Electrolysis through this electrode revealed no (111) or only partial (210 and 304) destruction of the NA. Also, such destruction did not affect or only partially blocked the bradycardia on NS stimulation, depending on the proximity to the nucleus.

**Table 2. Effects of destruction of the dorsal motor nucleus of vagus on bradycardia on stimulation of nucleus solitarius and nucleus ambiguus**

<table>
<thead>
<tr>
<th>Cat No.</th>
<th>Solitarius stimulation before lesion</th>
<th>Ambiguous stimulation before lesion</th>
<th>Solitarius stimulation after lesion</th>
<th>Ambiguous stimulation after lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td>621*</td>
<td>194 – 110 (-84)</td>
<td>198 – 32 (-166)</td>
<td>200 – 205 (-4)</td>
<td>206 – 30 (-179)</td>
</tr>
<tr>
<td>115</td>
<td>220 – 108 (-112)</td>
<td>220 – 72 (-148)</td>
<td>222 – 222 (0)</td>
<td>222 – 70 (-152)</td>
</tr>
<tr>
<td>209</td>
<td>222 – 122 (-110)</td>
<td>223 – 114 (-118)</td>
<td>224 – 198 (-26)</td>
<td>224 – 110 (-114)</td>
</tr>
<tr>
<td>414</td>
<td>218 – 106 (-112)</td>
<td>218 – 84 (-134)</td>
<td>220 – 222 (+8)</td>
<td>220 – 84 (-106)</td>
</tr>
<tr>
<td>425</td>
<td>210 – 130 (-85)</td>
<td>212 – 124 (-98)</td>
<td>220 – 220 (0)</td>
<td>220 – 124 (-96)</td>
</tr>
<tr>
<td>511</td>
<td>222 – 120 (-112)</td>
<td>232 – 100 (-132)</td>
<td>240 – 220 (-20)</td>
<td>238 – 116 (-125)</td>
</tr>
<tr>
<td>722</td>
<td>184 – 92 (-192)</td>
<td>196 – 60 (-116)</td>
<td>210 – 210 (0)</td>
<td>210 – 98 (-112)</td>
</tr>
<tr>
<td>801</td>
<td>226 – 122 (-104)</td>
<td>226 – 114 (-112)</td>
<td>226 – 192 (-34)</td>
<td>226 – 118 (-106)</td>
</tr>
</tbody>
</table>

Values are resting heart rate - maximum change of heart rate during stimulation. Numbers in parentheses are the extent of cardiac response. +, Increase. -, Decrease. * Tracings of this cat are shown on Fig. 2.

**Discussion**

The vagal pathway for cardioinhibition is complicated and the relationships between the NS, DNV, and NA have not been fully understood. Cardiovagal fibers arise principally from the same side of the medulla. This is not the case for the relationships between the NS, DNV, and NA, which have not been fully understood. Cardiovagal fibers arise principally from the same side of the medulla.
evident in the present experiments, in that unilateral vagotomy completely abolished the bradycardia on stimulation of the NS and NA of the same side. This finding is consistent with the recent findings of Thomas and Calaresu (27) but not with those of Gunn et al. (12) and Calaresu and Pearce (4). The latter investigators observed a partial abolition of the bradycardia on stimulation of the NS after ipsilateral vagotomy. These investigators probably stimulated the NS located in the medial extension (commissural nucleus of Cajal) merging with the contralateral NS, since they also observed complete abolition of the bradycardia subsequent to ipsilateral vagotomy when the stimulation site in the NS was found rostral to the commissure. Therefore, the discrepancy of findings with respect to whether ipsilateral vagotomy would completely eliminate NS-induced bradycardia may not be a matter of different methods or parameters of stimulation, but of whether the commissure is involved. As a matter of fact, in these experiments the parameters of stimulation were essentially similar to those of Gunn et al. (12). The results, however, were not identical.

In the present investigation, stimulation of the NS and NA produced marked bradycardia. A single discrete

![Fig. 3. Effect of NA lesion on NS bradycardia. Two electrodes were placed on NS and NA (arrows). Neither NS or NA bradycardia was altered by contralateral vagotomy. After electrolysis of NA through same stimulation electrode, stimulation of NS no longer produced any cardiac slowing, even when intensity of stimulation was increased to 8 V.](https://example.com/fig3.png)
Table 4. Effects of electrolysis of ventral midline area on bradycardia on stimulation of nucleus solitarius

<table>
<thead>
<tr>
<th>Cat No.</th>
<th>Heart Rate, beats/min</th>
<th>Ratio of bradycardia</th>
<th>Heart Rate, beats/min</th>
<th>Ratio of bradycardia</th>
</tr>
</thead>
<tbody>
<tr>
<td>322*</td>
<td>218 - 96 (-122)</td>
<td>62/122 = 51%</td>
<td>210 - 148 (-62)</td>
<td>56/122 = 46%</td>
</tr>
<tr>
<td>330</td>
<td>224 - 102 (-122)</td>
<td>98/132 = 74%</td>
<td>230 - 174 (-56)</td>
<td>98/132 = 74%</td>
</tr>
<tr>
<td>508</td>
<td>198 - 66 (-132)</td>
<td>64/120 = 53%</td>
<td>198 - 100 (-32)</td>
<td>64/120 = 53%</td>
</tr>
<tr>
<td>709</td>
<td>214 - 94 (-120)</td>
<td>70/112 = 63%</td>
<td>220 - 156 (-64)</td>
<td>70/112 = 63%</td>
</tr>
<tr>
<td>713</td>
<td>200 - 88 (-112)</td>
<td>88/138 = 64%</td>
<td>192 - 122 (-70)</td>
<td>88/138 = 64%</td>
</tr>
<tr>
<td>814</td>
<td>230 - 92 (-138)</td>
<td>88/138 = 64%</td>
<td>220 - 132 (-88)</td>
<td>88/138 = 64%</td>
</tr>
</tbody>
</table>

Values are resting heart rate - maximum change of heart rate during stimulation. Numbers in parentheses are the extent of cardiac response. +, Increase. -, Decrease. *Tracings of this cat are shown in Fig. 4.

Lesion in the NA largely or completely abolished the NS bradycardia. However, an extensive NS and or DNV lesion did not affect the bradycardia on stimulation of the NA. Destruction of the DNV eliminated the bradycardia induced by NS but not by NA stimulation. Since destruction of the distal nucleus always blocked the bradycardic effect of the proximal one, the logical sequence of order of these three vagal nuclei in the cardioinhibitory pathway should be NS, DNV, and NA. One may probably be suspicious that the abolition of bradycardia on NS or DNV stimulation subsequent to electrolysis of NA may be a result of the spreading of the current to the NS or DNV. This does not appear very likely as judged by the following evidence. 1) When two electrodes were simultaneously placed in the NS and NA, electrolysis of the NS did not affect the bradycardia on NA stimulation. 2) Electrolysis of the area adjacent to the NA without actual involvement of the nucleus itself did not affect the bradycardia induced by NS stimulation (Table 3, cat III). It should be noted that the NA is an elongate structure extending almost through the whole medulla. In the present experiments, when the stimulation and ablation sites were confined to an area 1-3 mm rostral to the obex and the electrodes were introduced vertically to the surface of the medulla, a discrete lesion in the NA over a rostrocaudal extent corresponding to that of the NS abolished the ipsilateral NS-induced bradycardia. This finding may indicate that
cardioinhibitory neurons are not diffusely distributed throughout the whole NA. This is in agreement with the previous findings of Lee et al. (19) who have also shown that bilateral destruction of a single point on either the NS, DNV, or NA eliminated the bradycardia on the Bezold-Jarisch and baroreceptor reflexes.

The DNV has long been taken as the primary origin of vagal efferents to the heart. This concept has been challenged by Gunn et al. (12), Kerr (17), and Thomas and Calaresu (27). These investigators suggest that vagal efferents to the heart probably arise from the NA rather than the DNV, basing their concept on the following indirect evidence. 1) Electrical stimulation of the DNV rarely evoked cardiac slowing in the cat and dog, but marked bradycardia was always observed consequent to stimulation of the NS and NA. 2) Both electrophysiological (1, 9, 14, 22, 23, 26) and anatomical (8, 15, 16) studies have shown that the NS is the relay station for afferents from carotid sinus and aortic depressor nerves, and have excluded this nucleus as the origin of cardiac efferents. 3) The bradycardia subsequent to brain stem ischemia or to peripheral vagal stimulation persisted after destruction of the DNV in either acute or chronic preparation (2, 17). 4) After a lesion was made in the NS, degenerated axons were found projecting ventrolaterally to the NA (24), indicating the presence of second-order neurons from the NS to the NA. 5) The latent period of evoked vagal potentials after NA stimulation was shorter than that after NS stimulation (12).

Evidence from our present investigation supports the aforementioned contention regarding the NS as a sensory or afferent nucleus and the NA as a vagal cardioprotector or efferent nucleus. Moreover, not only did stimulation of the NA always produce pronounced bradycardia but puncture of the NA by the electrode alone produced intense bradycardia lasting from 30 min to more than an hour. This phenomenon has been described by Laborde (18) and used as a criterion for localization of the cardioinhibitory neurons. It is interesting to observe that puncture stimulation always produced prolonged bradycardia, since even with intense electrical stimulation the bradycardia ceased some seconds after the termination of stimulation. This seems to indicate that the cardiovagal motor neurons in the NA remain excited for a longer period after mechanical irritation than after electrical stimulation.

However, the DNV may not be entirely insignificant for cardioinhibition. Lee et al. (19) have shown that the reflex bradycardia elicited by the baroreceptor and Bezold-Jarisch reflexes depended as well on the integrity of the NS, NA, and DNV. Destruction of any one of these three nuclei including the DNV abolished the reflex bradycardia. Calaresu and Cottle (3) observed axonal degeneration in the intramedullary rootlets and in the cervical trunk of the vagus, including the cardiac branches, in cats after destruction of the DNV. Deiters (11) also reported that both the DNV and NA were connected to the vagus and glossopharyngeal nerves. The present investigation shows that a DNV lesion did not affect the bradycardia induced by stimulation of the NA, but largely or completely eliminated the NS bradycardia. This finding further supports the idea that the DNV is involved in the central cardiovagal pathway between the NS and NA. The validity of the abolition of the NS bradycardia by a DNV lesion, however, requires careful evaluation because of the proximity of these two nuclei. Data in which destruction of the DNV involved the NS were discarded. Lesions of the DNV by either micropipette suction or electrolysis gave the same result. This finding indicates that the DNV is probably involved in the central cardiovagal pathway between the NS and NA. However, electrical stimulation of the DNV elicits no discernible cardiac slowing, suggesting few or scanty synaptic connections within this nucleus. Another possibility is that the efferent fibers from the NS through the DNV region could be very resistant to electrical stimulation.

On the basis of the evidence discussed above a scheme of the central pathway mediating reflex bradycardia of vagal origin, i.e., baroreceptor and Bezold-Jarisch reflexes, is made. The afferent fibers from the above receptors synapse in the NS. The nature of this synapse is probably cholinergic (19). The fibers passing through the DNV likely have few synaptic connections. Thereafter the cardiovagal pathway for the baroreceptor reflex diverges to the ventral midline region, but that for the Bezold-Jarisch reflex proceeds directly to the NA (19). This may account for the partial elimination of the bradycardia consequent to NS stimulation after destruction of the ventral midline area, inasmuch as only part but not all the vagal pathways pass in this area. Finally, all the fibers synapse with the NA that gives rise to vagal efferents to the heart.

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