The Vomiting Center: Its Destruction by Radon Implantation in Dog Medulla Oblongata

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In previous publications (1, 2) we have demonstrated with two different tech-nics, that is, by electrical stimulation and with ablation by electrocautery, that the vomiting center is located in the dorsolateral portion of the reticular formation of the medulla oblongata. This finding is not in agreement with the contention of Hatcher and Weiss (3) that the dorsal sensory nucleus of the vagus constitutes the emetic center. We have also recently shown, in a corollary study, that a specialized chemoreceptor trigger zone for emetic agents such as apomorphine and digitalis is situated in the dorsolateral region of the ala cinerea (4).

The procedure used by us for cauterization of the reticular emetic apparatus (2) necessarily involved destruction of tissue in the floor of the fourth ventricle, including the dorsal vagal nuclei. The present experiments were designed to circumvent the objection that the extensive destruction with electrocautery does not permit an adequate differential analysis of function between these medullary regions. A technic for implanting radon seeds to produce discrete lesions in the medulla oblongata has been developed by us (5). By such means it is possible to make isolated lesions in the lateral reticular formation without disturbing periventricular structures.

It is the purpose of this report to present an investigation of the changes in emetic responsiveness of dogs subjected to operations for radon destruction of the emetic center. Standardized emetic tests of high potency, with known mechanisms of action and operating through different routes of administration were chosen for threshold studies (6).

METHODS

Thirteen dogs weighing from 7 to 10 kg. were used in this study. Before the operations for radon implantation were performed, all dogs were tested for emetic thresholds to intravenous apomorphine and intragastric copper sulphate. The details of these testing procedures have been reported elsewhere (2). Briefly, 0.01 mg/kg. of apomorphine hydrochloride was chosen for the initial emetic test; for this dose, the known incidence of vomiting in normal dogs is 37 per cent, with an average latency of 2 minutes. Depending on the result of the first test, a second test with twice or half the original dose was made on another day. The copper sulphate was given

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by stomach tube in a constant volume of 50 ml. of water after approximately 18 hours
of food deprivation. A dose of 4.0 mg/kg. (water of hydration not included in calcu-
lation) is known to induce emesis within 30 minutes in 85 per cent of the normal dogs
tested. This dose was used for a preliminary test and the dosage for succeeding trials
on different days was either doubled or halved according to the response in the initial
test. These procedures were repeated several weeks following radon implantation to
redetermine emetic thresholds. Several tests were also made with the cardiac glyco-
sides, lanatoside C and scillaren A. These were administered intravenously in known
emetic doses (4).

The use of radon for making lesions in the central nervous system has been de-
scribed in detail in another publication (5). The operation for destruction of the
vomiting center was performed with sodium pentobarbital as the anesthetic. With
the head ventroflexed, the caudal portion of the medulla was exposed and the radon
seed implanted with what is essentially a long hypodermic needle fitted with a stylet.
The needle was inserted through the dorsum of the spinal cord into the desired por-

cation of the medullary reticular substance and the seed, either gold or glass, was then
deposited by using the stylet as a plunger (fig. 1). This procedure was carried out
bilaterally in a single operation or in two stages with 1 to 2 months intervening.3

On completion of the experiment, the medulla was perfused in situ with 10 per
cent formalin. The brains were subjected to a variety of histological procedures in-
cluding sectioning by the paraffin, freezing and celloidin technics and staining with
hematoxylin and eosin, and the Nissl and Mahon methods.

RESULTS

The effects on vomiting responsiveness following implantation of radon seeds
in the medullary reticular substance of dogs are summarized in table 1. The animals
are classified in 4 categories according to the extent of functional impairment of the
emetic responses to intravenous apomorphine and intragastric copper sulphate.
Category a serves as a control for the experimental method. Dummy seeds were im-
planted with the same routine procedure as used for radioactive seeds. It is evident
that neither the dummy gold implants (dog 112) nor the dummy glass implants (dog
219) had any significant effect on emetic thresholds. Histological analysis of the

3 Penicillin and aureomycin were used during the postoperative course, and they were supplied
generously to us by Lederle Laboratories.
brains of these animals revealed that damage was very slight and was limited to the size of each seed (see fig. 2a).

In category b are included 4 dogs which showed no appreciable change of emetic thresholds after implantation of radon seeds containing adequate radiation doses. In each case it was found that the lesions were misplaced as judged from the localization of the vomiting center in stimulation experiments already reported (1) (indicated by crosses in fig. 2a). The lesions in dog 231 were not only smaller than anticipated but they were placed in the ventral portion of the reticular formation. Similarly, the lesions in dogs 162 and 221 were found to be incorrectly situated. Dog 237 (see fig. 2b) had fairly large lesions but that on the right side was too ventral and the one on the left side was too superficially placed.

In category c are dogs which showed moderate postoperative refractoriness to apomorphine and copper sulphate. The lesions in dog 172 were placed somewhat medially, touching the dorsomedial border of the lateral reticular formation. Dog 214 (see fig. 2c) showed the most symmetrically placed lesions; these were rather small and the damage on the left side was slightly too dorsal. Dog 305 had a very large lesion on the right side and the one on the left was small and medially placed.

![Cross sections of medulla oblongata](http://ajplegacy.physiology.org/DownloadedFrom)
In category d are animals which showed marked to complete refractoriness to emetic agents throughout the postoperative period. Dog 106 had fairly symmetrical lesions but the lesion on the left side was placed more rostrally than the right. This animal was the only one that survived simultaneous bilateral implantation of gold seeds larger than 0.4 mc. each. This dog could stand and walk but had to be fed parenterally for the duration of survival and it succumbed without vomiting 4 hours following the intragastric administration of 32 mg/kg. of copper sulphate on the 29th postoperative day. Dog 315 was the only dog that was completely refractory to 64 mg/kg. copper sulphate. This dog was also insensitive to 0.14 mg/kg. lanatoside C and 0.12 mg/kg. scillaren A given intravenously. However, it vomited to 0.15 mg/

**Table 1. Effects of medullary radon seed implantation on emetic responses to intravenously administered apomorphine and orally administered copper sulphate**

<table>
<thead>
<tr>
<th>DOG NO.</th>
<th>RADON</th>
<th>APOMORPHINE HYDROCHLORIDE, I.V.</th>
<th>COOPER SULPHATE, ORALLY</th>
<th>SURVIVAL TIME</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>type</td>
<td>Preoperative</td>
<td>Postoperative</td>
<td>Preoperative</td>
</tr>
<tr>
<td></td>
<td>mc.</td>
<td>Threshold</td>
<td>Latency</td>
<td>Threshold</td>
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<tr>
<td></td>
<td></td>
<td>mg/kg. min.</td>
<td></td>
<td>mg/kg. min.</td>
</tr>
<tr>
<td>a) 112</td>
<td>Gold</td>
<td>.02 1</td>
<td>.02 2</td>
<td>.09 2</td>
</tr>
<tr>
<td>219</td>
<td>Glass</td>
<td>.02 1</td>
<td>.02 1</td>
<td>.02 1</td>
</tr>
<tr>
<td>b) 221</td>
<td>Gold</td>
<td>.04 1</td>
<td>.04 2</td>
<td>.05 2</td>
</tr>
<tr>
<td>162</td>
<td>Glass</td>
<td>.005 .02 1</td>
<td>.02 2</td>
<td>4</td>
</tr>
<tr>
<td>221</td>
<td>Gold</td>
<td>.03 .02 1</td>
<td>.02 2</td>
<td>4</td>
</tr>
<tr>
<td>237</td>
<td>Glass</td>
<td>.001 1.5</td>
<td>.02 2</td>
<td>4</td>
</tr>
<tr>
<td>c) 171</td>
<td>Gold</td>
<td>.02 .02 1</td>
<td>.02 2</td>
<td>.02 2</td>
</tr>
<tr>
<td>314</td>
<td>Glass</td>
<td>.001 .02 1</td>
<td>.02 2</td>
<td>4</td>
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<tr>
<td>605</td>
<td>Glass</td>
<td>.002 .05 1</td>
<td>.02 2</td>
<td>4</td>
</tr>
<tr>
<td>d) 166</td>
<td>Gold</td>
<td>.06 .01 2</td>
<td>.02 2</td>
<td>.02 2</td>
</tr>
<tr>
<td>315</td>
<td>Gold</td>
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<tr>
<td>44</td>
<td>Glass</td>
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<td>4</td>
</tr>
<tr>
<td>302</td>
<td>Glass</td>
<td>.005 .02 1</td>
<td>.02 2</td>
<td>4</td>
</tr>
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1 Seeds were implanted serially in 2 operations. 2 Retched but did not vomit.

Recent developments in the therapy of motion sickness have stimulated new interest in the central mechanism of vomiting. The location of the vomiting center
is no longer merely an academic question but it has become one of practical importance in the rational use of drugs for the clinical relief of vomiting. The discovery of the chemoreceptor trigger zone for emesis, dorsal to the emetic center (4), calls for a re-evaluation of 'central' emetic drugs and it makes a revision of the traditional concept of the nervous control of vomiting imperative.

In experimental neurophysiology relatively few problems are encountered in placing lesions within surface structures of the central nervous system. However, the blind orientation and preset regulation of damage which are necessary for attackng subsurface loci make this type of ablation, particularly for deep and vital brain structures, a formidable task. Several standard techniques are available for deep tissue destruction; namely, mechanical ablation, injection of caustic chemicals, thermocoagulation, electrolytic fulguration, freezing and suction. Most of these, however, are limited in application to gross ablation of nonvital structures because of certain objectionable features largely referable to the degree of trauma and extent of surface damage which they cause.

The advantages of a temporary radioactive source, such as radon, for making lesions in the central nervous system are manifold. a) The size of the lesion may be predicted with fair accuracy. b) The lesion growth is slow and progressive, thus permitting compensatory processes to take effect over a number of days during the onset of motor deficiencies. c) Large deep lesions of complex form can be made with negligible damage to surface tissue. The use of radon was particularly advantageous in this series of experiments because it was suitable for making a cylindrical lesion in the lateral reticular formation of the medulla oblongata without damaging the periventricular tissue. The particular intent was to impair the execution of emesis regardless of the source of the stimulating influence by destroying the vomiting center while sparing the dorsally situated chemoreceptor trigger zone. This was accomplished by approaching the vomiting center through the dorsum of the spinal cord as indicated in figure 1.

Generally, lesions obtained with glass radon seeds (β radiation) are more sharply circumscribed than those resulting from gold seed implantation (γ radiation) (5). We have found, however, that glass seeds are more difficult to place accurately because they tend to adhere to the trocar when it is withdrawn from the brain substance.

Edema of the brain is an acute reaction to all forms of applied radiation. Consequently, simultaneous bilateral implantation of radon seeds in the medulla causes edema on both sides with attendant widespread functional impairment. We have found that the maximum tolerated radiation for long term survival after simultaneous bilateral implantation in the medullary reticular formation is 0.4 mc/seed for gold implants and 0.015 mc/seed for glass implants. It has been possible to elevate somewhat the maximum tolerated dose by performing the implantation in two stages to permit the swelling on the one side to subside before implanting the radon in the opposite side.

It is common practice by many clinicians to consider retching and vomiting as equivalent phenomena. We have pointed out in previous publications (7, 8) that not only can retching and vomiting be differentiated in the physiology laboratory but
that separate loci regulate these functions and serve as the anatomic basis for the clinical differentiation of labored and projectile vomiting. The question assumes important proportions because we have found in one dog (dog 64) with a radon ablated emetic center that a normally effective dose of lanatoside C yielded nonproductive retching; that is, no expulsion of vomitus occurred despite the fact that the animal had eaten prior to being tested (see also table I). It is therefore to be re-emphasized that retching is not justifiably used as the equivalent of vomiting.

An outstanding feature of the medullary reticular formation is its diffuse and homogeneous character. Nevertheless, it is well known and widely accepted that distinct portions of the reticular substance comprise the respiratory and vasomotor centers. Likewise, the vomiting center despite its lack of morphologic boundaries is situated in a rather limited portion of the lateral reticular formation. This fact is quite evident from the results obtained with radon implantation. Two points should be stressed: 1) dog 237 illustrates that large inaccurately placed lesions do not seriously impair vomiting; and 2) dog 214 illustrates that small lesions accurately placed in the emetic center are effective in appreciably raising the emetic threshold. Thus, the size of the lesion cannot be used as a substitute for accuracy in the localization of the emetic center. On the other hand, the difficulty in completely destroying the emetic center is not to be minimized. Indeed, the amorphous quality of the vomiting center has been the chief deterrent to its precise localization by earlier workers.

SUMMARY AND CONCLUSIONS

Slowly progressive lesions were effected by radon seed implantation in the interior of the medulla oblongata without injury to the periventricular gray. The lesions were relatively discrete and the extent of the damage was predictable. Dogs with such lesions placed accurately and bilaterally in the dorsolateral portion of the reticular formation showed no response to the intravenously administered apomorphine and were also refractory to large doses of copper sulphate given via the gastric route. Thus, the location of the vomiting center is further confirmed to be in the medullary reticular formation.

REFERENCES