An Experimental Evaluation of the Effects of Subarachnoid Injection of Phenol-Pantopaque in Cats  
A Histological Study*  

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This study was undertaken in an attempt to explain certain puzzling phenomena observed in the clinical use of injections of phenol. We had noted the incongruity of relief of subjective pain without diminution of sensibilities of pain and touch as tested for in the usual neurological examination. Others observing this phenomenon had hypothesized this was the result of selective destruction of the smaller fibers but histological verification of this hypothesis has not appeared in the literature. Furthermore, we sought an answer as to why, in spite of a uniform procedure, the results of injections of phenol often were unpredictable and, even more disturbing, why there often would be an early recurrence of pain or spasticity after what appeared initially to be a successful injection.

Satisfactory human material for this study was not available from our clinical series as the conditions treated were chronic and patients either died at home or in most instances are still alive. The few cases available for pathological study were unsuitable for evaluating the histological changes wrought by the phenol, as the condition treated might well of itself have brought about the changes observed in the spinal cord or roots.

Method

Twenty-nine adult cats, weighing 2-2.5 kg., were operated upon following anesthetization with intraperitoneal Nembutal. A lumbar laminectomy was performed and the material to be tested was injected by direct visualization into the subarachnoid space. Materials for testing were prepared by dissolving phenol crystals in Pantopaque in strengths of 1:10, 1:15, and 1:20. Each animal to be tested was injected with 1/10 cc. of the solution and so positioned as to layer this material onto the right-sided roots of the cauda equina. Controls consisted of 3 cats injected subarachnoidially with absolute alcohol and positioned head-down, 3 cats with surgical posterior rhizotomy, 1 cat subjected to a sham procedure with isolation but not section of a posterior root, and 2 cats injected with Pantopaque alone. The effects of phenol on “gamma” hypertonicity3,5 were studied by layering 1:10 phenol-Pantopaque against the cervical roots in 3 cats rendered decerebrate by an intercollicular section. Injected animals were kept in the experimental position for at least 1 hour to allow for full reaction of the phenol with the nerve roots.

Chronic animals were observed daily for motor and sensory changes. Those selected for histological study were anesthetized on the 7th to 10th postoperative day and perfused with 15 per cent formalin. The brain and spinal cord were preserved in fresh 15 per cent formalin (changed frequently) for 2 to 5 months. Frozen serial sections of the spinal cord and roots were cut at 15 and 25 µ in transverse, sagittal, and horizontal planes, stained using the Nauta-Gygax23 technique and examined microscopically. The patterns of degeneration were plotted on drawings of transverse, sagittal, and horizontal spinal-cord sections and photomicrographs were taken of representative fields of degeneration.

Observations

Physical. Immediately following injection of 1:10 and 1:15 solutions of phenol around the cauda equina there appeared a rhythmic twitching and jerking of the right hind limb. This movement was more marked with the stronger (1:10) solution and usually lasted 5 to 10 min. It is likely this movement caused some undesired dispersion of the phenol-Pantopaque solution and might account for some of the histological findings to be described below.
There was little difference in the reactions of the phenol-treated as compared to the control cats when they were challenged during the postoperative period with such noxious stimuli as pin prick, firm periosteal pressure, and intracutaneous injection of histamine.

Motor deficit was obvious in the cats treated with 1:10 phenol. There were weakness and hypotonia in both hind limbs, more marked on the "down" or right side, and the patella and ankle reflexes were diminished to absent. The placing reflex was absent in the lower limbs. All motor deficit cleared by the 7th postoperative day. Animals treated with 1:15 phenol showed similar but less severe deficit. One cat of this group, however, was weak in all limbs and had no stretch reflexes for several days after the injection. Another cat showed weakness and an absent placing reflex only in the right hind limb. In both of these latter cats the deficit disappeared by the 7th postoperative day. There was no demonstrable motor deficit in the cats injected with 1:20 phenol-Pantopaque. In 3 decerebrate cats the 1:10 phenol-Pantopaque caused an obvious diminution in the extensor rigidity of the forelimbs. This was less noticeable after 30–45 min. and the full measure of rigidity had recurred some 4 hours after the injections.

*Histological.* It was apparent on examining the silver-stained sections of the spinal cord and roots that greater destruction had been wrought by the more concentrated solution (1:10) and the damage was, as expected, more severe on the dependent side. Somewhat unexpected, however, was the capricious manner in which the phenol had acted. The various concentrations of phenol appeared to differ more in a quantitative than a qualitative manner in their action of selective destruction of fibers. Thus, in any section taken from the lumbar or sacral cord evidence of degeneration in all fiber-size groups was present and yet, in the same section, there were intact small and large fibers adjacent to the degenerated fibers (Figs. 1 and 2).

A similar distribution of degenerated fibers was seen with all concentrations of phenol tested (Figs. 3 and 4). The majority of the degenerated fibers entered the posterior columns through the dorsal and medial margins, although a few small fibers were seen coursing through the zona spongiosa to fields of preterminal degeneration which were present in the substantia gelatinosa and nucleus proprius. Degenerated axones of various sizes could be followed to zones of degenerated preterminal elements located in sensory, internuncial, and motor groups of cells of the ipsilateral sacral and lumbar spinal cord. Other degenerated fibers were observed to pass to the opposite side of the cord. In more rostral sections degenerated fibers were found in the fasciculi gracilis and proprius.

Degenerated axones in the proximal dorsal root were more abundant in the periphery of this structure, as though the action of the phenol was in part dependent on a surface phenomenon (Figs. 5 and 6).

The alcohol-injected controls showed a more profuse degeneration of axones (Fig. 7) than did the cats injected with 1:10 phenol (Fig. 1). Again, fibers of all sizes were involved but with alcohol there was profuse degeneration as any given root-entry zone would show almost total destruction. The pattern of terminal distribution of the degenerated fibers in the ipsilateral cord at the level of the injection and at more rostral levels was similar to that described for the phenol-injected animals (Fig. 8).

Sections of the cord at the level of a surgical posterior rhizotomy revealed degeneration of all but a few fibers at the root-entry zone. The few intact fibers likely represent fibers entering from adjacent levels. There was a pronounced increase in the number of degenerated small fibers seen in the tract of Lissauer in the surgical-rhizotomy group (Fig. 9) when compared to the phenol-injected cats (Fig. 10). The intact tract of Lissauer on the side contralateral to the surgical rhizotomy is shown in Fig. 11. The dorsal roots and root-entry zones of the control animals with the sham operation or injection of Pantopaque showed no evidence of axonal degeneration.
Critique of Method. The protocol for this experiment was designed to simulate the clinical conditions as closely as possible. However, radiological confirmation of the placement of the phenol-Pantopaque solution was not done in these experiments. Histological examination of the spinal cord and roots indicated the phenol was more widely dispersed in these experiments than we would expect it to be in the clinical situation. However, the volume used in these experiments was greater proportion-
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FIGS. 3 and 4. Drawings of cross sections of spinal cord at a high sacral level. (Above) This depicts the usual degeneration seen with 1:10 phenol. Degenerated fibers are represented by small dashes. The distribution of the fibers within the central grey matter indicates that fibers ending in all groups of cells were involved. Some degeneration was present on the opposite side of the cord. (R) Right side of cord.

(Below) This shows the usual pattern of degeneration with 1:20 phenol. The distribution of degeneration is very similar to that seen in the 1:10 animals but the amount of axonal degeneration is much less.

Fig. 5. Drawing of horizontal section of a proximal dorsal root to illustrate the predominance of degeneration of fibers along the periphery of the root. (G) Ganglion cells.

Fig. 6. Photomicrograph (Χ1665) of a region in the periphery of a proximal dorsal root exposed to 1:10 phenol. Both large and small fibers showing evidence of degeneration are seen to be running adjacent to fibers of similar size which are still intact. (a) Degenerated small fiber. (b) Degenerated large fiber. (c) Intact small fibers. (d) Intact large fiber.
reliability of our observations made of degenerated fibers in the dorsal roots.

One-tenth cc. of 1:10 phenol-Pantopaque was injected into the caudal subarachnoid space of 4 cats, and in each animal a surgical section of a thoracic posterior root was performed. The tissues thereafter were handled in a fashion identical to that described in the experimental protocol. Blocks of the chemically treated roots, the sectioned thoracic root, and an intact high cervical root were cut and stained simultaneously.

Photomicrographs of these sections are shown in Figs. 12, 13 and 14. No degeneration can be seen in the fibers of the cervical root (Fig. 12). The classical signs of degeneration, formation of droplets and disruption of continuity of fibers, are readily apparent in the sectioned root shown in Fig. 13. A root treated with phenol-Pantopaque solution is shown in Fig. 14 and here the degenerated fibers lie predominantly at the periphery of the root, and are intermingled with many intact fibers.

These observations indicate the Nauta-Gygax technique is applicable for the study of degenerated axones in the dorsal roots.

Discussion

The rationale for the use of phenol to produce a selective permanent chemical rhizotomy is based on the hypothesis that in dilute solution the phenol might act in a fashion similar to a local anesthetic, and affect primarily small fibers. That is, the dilute phenol will destroy "C" fibers and A-delta and A-gamma fibers without inducing severe damage to the groups of large fibers. However, as noted by Gasser and Erlanger in their original studies on the selective effect of cocaine on peripheral...
nerves, even the local anesthetics are not completely selective, for they state "The sum of the experiments shows that in general small fibers are blocked before large ones, but that the blocking is not effected with any precision. Fibers of all sizes are found to be unable to conduct as long as smaller ones. Thus, while fiber size is a determining factor in nerve susceptibility to poisons, it is not sufficiently differentiating to cause the fibers to drop out on a strictly size-basis. It may be for this reason that the psycho-physiological findings are not in better accord."
There are factors other than size of fibers that probably play an important role in the "nonselectivity" of phenol as employed clinically. Certain mechanical factors difficult to control are present. The phenol does not affect the roots until it diffuses from the Pantopaque and enters the aqueous phase.

The concentration of this aqueous solution and the area of nervous tissue over which this effective concentration is exposed is variable as the Pantopaque becomes globulated. In addition currents of cerebrospinal fluid undoubtedly are not constant from moment to moment, nor from patient to patient. Therefore, the "nonselectivity" probably must be explained on this basis.
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Iggo and Walsh⁴ and Nathan and Sears,¹¹ using electrophysiological techniques, have studied the selective-block phenomenon of various solutions of phenol. They observed that the response of the “C” fibers was

...patient. Furthermore, because of the viscosity of the Pantopaque, it is doubtful if the active agent bathes the dorsal-root ganglia, hence the likelihood of permanent destruction of the sensory fibers is diminished.

FIG. 13. Photomicrograph (×495) of a section of a cut thoracic dorsal root, showing the total destruction of all axones.

FIG. 14. Photomicrograph (×190) of a spinal root exposed to 1:10 phenol-Pantopaque solution. Degenerated fibers intermingled with intact fibers are present along the periphery of the root.
effected earlier and to a greater extent than that of the larger fibers, but once the state of complete block of "C" fibers had been reached, the response of the "A" fibers also had been altered significantly.

This study offers a histological explanation for the above observed phenomena. Dilute phenol-Pantopaque does not effect a selective chemical rhizotomy as used clinically or as in this study for its toxic action appears dependent on factors other than size of the fibers. Concentrated solutions of phenol cause greater destruction, but even with the higher concentrations large numbers of fibers of all sizes remain intact. These findings also offer a possible explanation for the results seen in our clinical series. The treatment of intractable pain by surgical posterior rhizotomy is often an "all-or-none" response. That is, if the area of pain is not denervated totally by the rhizotomy, the pain usually will recur. The same phenomenon obtains in the treatment of spasticity by anterior rhizotomy. Again, if the affected muscles are not denervated completely the spasticity will recur gradually. Our studies would suggest that to destroy completely the pain-carrying fibers in the dorsal roots or the gamma-efferent fibers in the anterior roots with phenol-Pantopaque, it probably is necessary to destroy the entire root in a manner such as is accomplished with accurate surgical rhizotomy or with absolute alcohol.

Summary

1. Phenol-Pantopaque injected subarachnoidally in cats does not cause a selective destruction of smaller fibers in the roots or cord.

2. The apparent lack of a spectral susceptibility to the toxic action of phenol-Pantopaque may be caused by certain physical factors. Whether these factors rather than a mere indiscriminate effect of phenol regardless of the size of fibers account for the capricious action of this agent could not be ascertained from this study.

3. The over-all degree of destruction of fibers is related to the concentration of phenol-Pantopaque employed.

4. The histological findings in this study likely explain the unpredictability of phenol-Pantopaque as employed in our clinical series for the treatment of pain or spasticity.

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References


