HISTOLOGICAL FINDINGS FOLLOWING INTRATHECAL INJECTIONS OF PHENOL SOLUTIONS FOR RELIEF OF PAIN

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SUMMARY

The nervous system from nineteen patients with malignant disease who had intrathecal injections for the relief of pain was examined. In eighteen patients one or more injections of phenol in iophendylate or glycerol had been given; in six of them injections of silver nitrate and phenol in iophendylate or glycerol were also given. In one patient a single injection of silver nitrate and phenol in glycerol had been given. Material was also examined from eleven cats which had phenol in iophendylate applied to posterior nerve roots. The histological findings in one of these cats are described here. A control series of spinal cords from forty patients with malignant disease of the pelvic organs or lower limbs who did not receive intrathecal injections was also examined. The main findings were as follows: (1) Phenol in iophendylate or glycerol causes degeneration of both large and small nerve fibres. (2) The phenol acts on the fibres in the nerve roots and not on the ganglia or the spinal cord. (3) Posterior root degeneration was found in all the injected cases. It is concluded that at least some of this degeneration in each of the injected cases is due to the injection. (4) No evidence of excessive pathological reactions due to the injected solutions was found, with one exception. In this patient, who received a single injection of silver nitrate in phenol in glycerol, meningitis developed and led to death forty hours later.

In 1955 Maher reported a new form of intrathecal therapy for relieving pain caused by incurable cancer, further observations and slight modifications of the method being published later (1957, 1960). Maher injected phenol dissolved in oily solution in such a way that it should affect the posterior root fibres between their ganglia and the spinal cord. Phenol dissolved in glycerol or in iophendylate, an inert radio-opaque substance, proved to be the most satisfactory; occasionally silver nitrate was added. The pain was reported as being relieved in about half to two-thirds of the patients; and there were minimal side-effects. The results obtained by Nathan and Scott (1958) and Brown (1958) have been similar to those of Maher.

In view of the clinical findings it was obviously important to examine the central nervous system from patients who had had intrathecal injections of phenol in iophendylate or glycerol in order to find out the following points: whether these injections had caused any histological changes or not; whether the changes, if any, were confined to certain specific neurones or nerve fibres, and in particular the unmyelinated fibres; and what was the site of action of the phenol, in relation to the posterior root ganglion, the nerve roots and the spinal cord.

Degeneration of nerve fibres was in fact found to be present in every case examined, but there were considerable difficulties in deciding whether this degeneration was due to the phenol or to the neoplasm from which the patient died. Two further studies were therefore undertaken to try to clarify these points. The likelihood of finding degeneration in the central nervous system of patients with malignant disease who were not treated by intrathecal injections was established by examining the spinal cords from forty such patients. The findings in these cords supported the view that much of the degeneration in the central nervous system of patients who had been treated by intrathecal injections of phenol must be due to the injections. But to distinguish between
the degeneration due to the injection and that due to involvement of nervous tissue in the malignant growth still presented difficulties. In order to establish positively what are the histological changes occurring in healthy nervous tissue when the phenol solution is applied intrathecally, material from cats, in which the solution was applied after a laminectomy, was examined. This is being reported in another paper (Nathan, Sears, and Smith, 1964). The present paper reports the histological findings in patients who had been treated by intrathecal injections of phenol in iophendylate or glycerol for the relief of pain due to malignant disease, in a control series from patients who had not been so treated, and in one cat.

Since this study was completed, a paper has been published reporting the histological findings after therapeutic injections of phenol solutions in man (Berry and Olszewski, 1963), and two papers on the changes following injections in cats (Baxter and Schacherl, 1962; Stewart and Lourie, 1963). The findings reported in these papers will be discussed later.

**MATERIAL AND METHODS**

The central nervous system from nineteen patients who died from malignant disease and who had had intrathecal injections to relieve their pain was examined. In sixteen the injections had been made in the lumbo-sacral region, in one in the thoracic region, and in two in the cervical region. Eighteen of the patients had one or more injections of phenol in iophendylate or in glycerol. Six of them also had injections of silver nitrate and phenol in glycerol. One patient had a single injection of silver nitrate and phenol in glycerol.

One to 1.5 ml of the phenol solution in concentrations of 5–8 per cent were usually given at one time. The silver nitrate was used in concentrations of 1/100–1/60 grain (0.6–1 mg) in 4 per cent phenol in glycerol. The periods of survival of the patients after the injections varied from forty hours to twenty-two months. The majority of the injections had been given within six months of death.

In six patients the spinal cord with the relevant nerve roots and posterior root ganglia, and in the remaining thirteen patients only the spinal cord with the attached proximal parts of the spinal roots, were available for study. The cords were examined mostly in transverse sections, but in some instances in coronal, the nerve roots in the longitudinal and transverse sections, and the ganglia in longitudinal. In one case the cord from the second lumbar segment caudally, the cauda equina, and the posterior root ganglia were removed in continuity without opening the meninges; after fixation the tissue was divided into four blocks and these were sectioned in the coronal plane, complete interrupted series of sections being stained.

The nervous system from eleven cats was examined. In these, a drop of phenol in iophendylate was applied to one or more nerve roots exposed by laminectomy and incision of the dura. This open operation was essential because, owing to the absence of a true cauda equina in the cat, direct intrathecal injections would tend to damage the cord. The intention was to make the conditions as comparable as possible to the therapeutic procedures in man. These experiments were carried out by Nathan and Sears and they are reported in full in association with these authors (Nathan, Sears and Smith, 1964). In cat 17, with a survival period of six days, the last four lumbar segments, the sacral segments and the relevant nerve roots and ganglia were removed and embedded in one block; this block was sectioned in the coronal plane, complete interrupted series being taken. This cat is described here.

Most of the tissue, both human and cat, was embedded in celloidin, a few blocks were embedded in paraffin, and a few used for frozen sections. The methods used in the preparation of the sections included the following: haematoxylin and van Gieson, haematoxylin and eosin, thionin, phosphotungstic acid haematoxylin, Haggqvist, Loyez, Weigert-Pal, Gros-Bielschowsky, Nauta and Marchi.

Sections from the spinal cord from 40 patients who had malignant disease of the lower limbs or pelvic organs, and who were not treated by intrathecal injections of phenol in iophendylate or glycerol were also examined. These form a control group for the sixteen injected patients in whom the spread of the neoplastic tissue was similar, and in whom the injections had been given in the lumbar region. Diagrams of the cords from the forty control, and from the sixteen injected patients are presented for comparison.
RESULTS

CAT MATERIAL

As all abnormal findings in the cats are due only to the effects of the phenol solutions, the histological findings in the cat will be described first.

In cat 17, which had the shortest period of survival, six days, the phenol in iophendylate had been applied to the first sacral posterior root on the left. There are areas along both the posterior and anterior nerve roots where the normal structure of the nerve fibres has been lost and there is a very marked increase in vascularity. There appears to have been complete destruction of all the fibres of a rootlet at some of these areas (figs. 1A, C, D); in other areas only a few fibres are involved, often along the contiguous faces of adjoining rootlets (figs. 1E, F). The appearance of a normal rootlet is shown for comparison in figure 1B. These areas of marked inflammation and altered fibres would appear to be the site of action of the phenol in iophendylate. The nerve fibres are greatly swollen, distorted, and displaced by dilated vessels and perivascular cells. These fibres are obviously degenerating. Many of them consist of Schwann tubes containing pale-staining myelin, axis cylinder debris and foam cells; there is a marked increase in the number of Schwann cells, many showing mitosis. Fibres can be traced from the site at which they are damaged, by their obvious Wallerian degeneration; there is no marked distortion of the degenerating fibres, and the vascular reaction is much less marked than in the areas of local destruction described above. The posterior rootlets just before their entrance into the cord (fig. 1G) and the anterior root at the level of the posterior root ganglia (fig. 1H) show the most extensive Wallerian degeneration, with the least vascular reaction. Most of the fibres of the first left sacral roots and some of those of the second sacral roots are degenerating. A very few fibres are degenerating in more caudal roots.

Prominent inflammatory changes are evident in the meninges (fig. 1A). These are in part due to the operative trauma, as the meninges had to be opened to gain access to the roots. These changes are most marked at the proximal poles of the first and second left sacral ganglia at the region of the arachnoidal cul-de-sac. The epidural tissues contain some iophendylate, there is some fat necrosis, the vessels are congested and there are many polymorphonuclear leucocytes, some lymphocytes and foreign body giant cells in the tissue. Similar but less marked changes are present in the same distribution in the rest of the sacral segments and the sixth and seventh lumbar segments. Despite this very marked reaction in the surrounding tissues, direct damage to ganglionic cells is negligible, being confined to one ganglion (left S1) and affecting one or two cells only. A few fibres of the sensory root of this ganglion are degenerating very close to the ganglion, both on the surface and deeper in the root. Occasional vessels on the periphery of the ganglion appear to be dilated, but no abnormal nerve cells were seen in direct relation to them. Scattered throughout the first and second sacral ganglia there are pyknotic ganglionic cells, with an accompanying increase in the number of satellite cells (figs. 1H, I). These changes are most likely to be a reaction to the damage to the posterior nerve fibres. Pyknotic cells are not more frequent on the periphery than...
deeper in the ganglia. There appears to be an increase in the number of vessels on the surface of the cord, but there is no evidence of damage to the cord. In the anterior horn there is a considerable number of chromatolytic and of pyknotic cells, which indicate a reaction to the damage to the anterior nerve fibres. An examination of all the cats in the series confirms that there is no break in the continuity of affected bundles, although the nerve fibres themselves may be grossly altered.

The conclusion drawn from the findings in all the cats is that the phenol in iophendylate has caused degeneration in all the fibres with which it has come in contact, regardless of their size. The phenol has affected the rootlets not only at the main site of application but also patchily along their length. Fibres which have been destroyed at any part of their length by the action of the phenol undergo Wallerian degeneration in their distal part. The cumulative effect of all the lesions in the nerve bundle can be assessed central to that lesion which is closest to the cord in the case of the posterior root, and peripheral to that lesion lying furthest from the cord in the case of the anterior root. Direct damage to the neurones of the posterior root ganglia is insignificant, although the peri-ganglionic tissues show a marked inflammatory reaction. The changes seen in a very few neurones and the increase in satellite cells in the ganglia might possibly be due to the injected solution passing along the length of individual fibres into the depths of the ganglion itself, or they may be due to a retrograde reaction to damage of the posterior root fibres very close to the neurone.

The most important point which has been established in the cats is that degeneration of nerve fibres does, in fact, result from the application of phenol in iophendylate to a nerve root, and further, that large as well as small fibres are affected.

Eighteen patients with survival periods of three weeks to twenty months.

No difference was found at postmortem nor in the histological sections between the patients who had injections of phenol in iophendylate or glycerol and those who also had injections to which silver nitrate had been added; as the great majority of the injections were of phenol in iophendylate only, no distinction will be made in describing the histological findings with regard to the different solutions injected.

At postmortem the only findings which might be attributed to the injections were that some of the roots in the cauda equina were thinner and greyer than the others; and that occasionally they tended to separate into strands at some places. In some cases there was slight thickening of the leptomeninges in the lumbosacral region. There was no evidence of any marked meningeal reaction, of adhesions, of softening of the cord, nor of thrombosis of vessels. In thirteen patients no involvement of nerve roots nor ganglia in neoplasm was observed at postmortem; in the other five patients some degree of involvement was noted, in one being limited to the filum terminale.

The most striking histological finding has been that in every case there is definite and sometimes very marked degeneration of fibres in the posterior nerve roots and in the posterior columns. There are two possible causes for the posterior column degeneration in these cords; the degeneration could be due to neoplastic involvement of the posterior root ganglia, posterior roots or the cord itself; or it could be due to the action of the injected solution. The pathological changes seen in some of the cases will be described first, and then the evidence for attributing at least some of the changes to the intrathecal injections will be considered.

Cauda equina and ganglia.

In case Mrs. L. R., 2 ml of 8 per cent phenol in iophendylate had been injected two months before death, between the fourth and fifth lumbar vertebrae, the patient lying on her right side. It was known in this patient that the injected fluid had run rostrally as well as caudally, for radiographic examination just after the injection showed iophendylate as far rostral as the twelfth thoracic vertebra. The clinical findings had shown
that there was involvement in neoplasm of the fifth lumbar and all the sacral nerves on the right. At postmortem none of the posterior root ganglia and roots appeared to be involved in neoplasm, but histological examination revealed the invasion and partial destruction of the first and second right sacral ganglia.

The lumbosacral cord from the second lumbar segment caudally, the cauda equina, and posterior root ganglia were examined in serial coronal sections.

Many rootlets of the posterior nerve roots, and to a lesser extent of the anterior roots, show marked histological changes. These consist essentially of areas of degenerating fibres or of loss of fibres, accompanied by a vigorous cellular reaction. These areas tend to lie along the long axes of the nerve bundles, frequently affecting contiguous surfaces (figs. 2A, B, F). Rootlets of the right side from the second lumbar to the fifth sacral show this fibre change more extensively in the fourth and fifth lumbar roots than in the others. In no roots are all the rootlets affected and in most rootlets only a small proportion of the fibres are affected. These areas of well-defined fibre loss and degeneration have not been seen passing into the posterior root ganglia itself, although a few strings of cells and an occasional abnormal axon lying among normal fibres can be traced into the ganglia. In the anterior rootlets the most clear-cut areas of fibre loss lie near the cord.

Different stages of degeneration of fibres may be seen in adjoining rootlets and in different areas of the same rootlet. In most affected areas of both posterior and anterior rootlets all or most of the nerve fibres have disappeared (figs. 2B, F); occasionally a few disrupted and greatly swollen axons remain.

In a few places there is distinctive dense staining of "tubes" of Schwann cells and of small argentophilic debris, among which very fine fibres can occasionally be distinguished (figs. 2H, I). These appearances suggest regeneration of nerve fibres. As far as could be determined these changes are present only in the anterior roots. In juxtaposition with the areas of fibre loss lie normal fibres, large, medium and fine fibres, the last in groups, all being present (fig. 2J). Changes in the posterior root ganglia are slight except in the first and second right sacral where the distal part of each ganglion has been destroyed by neoplastic tissue (fig. 2E). There is consequently a generalized loss of nerve fibres in the posterior roots of these ganglia, which is easily distinguished by the absence of cellular or vascular reaction (fig. 2D) from changes due to the injection. In the right fourth and fifth lumbar ganglia (fig. 2C) there is a slight loss of neurones, and there appears to be a generalized increase in the number of non-neuronal cells which are probably reactions to the destruction of the posterior root fibres by phenol. No destruction by neoplastic cells was seen in the other ganglia and no evidence of inflammatory changes was seen in any of the ganglia.

For three reasons it appears that the patchy loss of nerve fibres described above is due to the injected solutions and not to the neoplasm.

(1) Both the distribution of the regions of fibre loss and the histological changes in these regions are similar to those seen in the cats.

(2) The only change in the rootlets which could be definitely deduced as being due to neoplastic involvement of the ganglia was a slight generalized fibre loss in two roots.

(3) The actual distribution of the fibre loss, with increasingly more fibres affected close to the cord in the posterior rootlets and increasingly more fibres affected peripherally in the anterior rootlets suggests destruction of the fibres in the rootlets themselves, rather than degeneration extending from a peripherally situated lesion.

It is important to trace the path taken by the injected solution as it leaves the needle, for this is a question which may affect the technique used by the operator. For this purpose serial sections of the whole of the cauda equina of this case were prepared. In spite of examining such a large number of serial sections, it has not proved wholly possible to determine the precise areas of actual destruction of fibres; the reason for this is that the length of survival was so long that the inflammatory reaction in the areas of destruction has died down and Wallerian degeneration is well advanced. However, three features of the distribution of the degenerated fibres support the view that the phenol solution has not only passed rostrally and caudally from the site of the injection,
FIG. 2 (contd.)

[See overleaf]
**FIG. 2 (contd.)**

A. Coronal section of lumbar cord and roots (sacral cord is not in plane of this section) and cauda equina from patient who had intrathecal injection of phenol in iophendylate two months before death (H. and V.G. x 1). The distribution of fibre loss thought to be due to phenol in iophendylate is indicated by black ink, along rootlets on right of figure. Tumour invasion indicated by TU.

B. Myelin preparation of rootlets showing regions of pallor due to loss of myelinated fibres, indicated by arrows (Loyez x 5).

C. Silver preparation of rootlet showing loss of axons on right (Gros-Bielschowsky and Nissl x150).

D. Posterior fibres from ganglion partially destroyed by tumour (H. and V.G. x 100).

E. Peripheral part of ganglion (S2) showing tumour (TU) and pale neurones (H. and V.G. x 140).

F. Posterior rootlets showing regions of fibre loss and cellular reaction along contiguous faces of rootlets (H. and V.G. x 100).

G. Part of ganglion (L3) showing residual cell nests (RCN) and dark-staining neurones (H. and V.G. x 140).

H. Anterior rootlet showing dark-staining Schwann tubes containing axon debris and very fine fibres (Gros-Bielschowsky and thionin x 80).

I. Enlargement of dark staining Schwann tubes from H (x 350).

J. Posterior fibres from region adjacent to zone of fibre loss showing groups of normal very fine fibres (Gros-Bielschowsky and thionin x 350).
but has run along the long axis of the rootlets, both centrally and peripherally, destroying the fibres with which it came in contact, possibly at a number of different sites along the length of any one root. These three features are:

(1) The fact that degenerated fibres have been seen in the whole length of some posterior rootlets, extending from near the ganglion right into the cord.

(2) The fact that degenerated fibres have been seen in adjacent anterior rootlets from near the cord to the distal ends of the roots.

(3) The fact that the maximum degree of degeneration is seen in the spinal cord end of the posterior root and the peripheral part of the anterior root.

These features can be explained only as being due to the cumulative effect of a number of destructive lesions along the length of the rootlets, each resulting in Wallerian degeneration. There is no evidence of any destruction of the posterior root ganglia by the injected solution. The pattern of destruction of fibres in this case may be summarized as follows. The phenol solution has destroyed all the fibres with which it has come into contact, regardless of their size. Contiguous fibres of adjoining rootlets are frequently affected. Destruction of the fibres has occurred without distortion of the rootlets. It has been followed by some increase in the formation of collagen within the area of fibre loss. Some regeneration of nerve fibres is proceeding. There is no evidence of direct destruction of the cell bodies of the posterior root ganglia by the injected solution. Changes in the ganglia have been limited to those which appear to be secondary reactions to lesions of the posterior roots caused by the injection, or to destruction of the peripheral nerves by malignant cells.

The lesions in this case are more scattered than in most of the other cases, but it has been used to illustrate the distribution of the lesions because the plane of sectioning is particularly well suited for this purpose. The findings in the other cases in which the roots and ganglia have been examined are similar to those described above, the number of roots affected, the extent of destruction of roots and of regeneration of fibres varying from case to case. Local destruction of ganglion cells has not exceeded a very few cells in any case. A few fibres have been seen to be degenerating back to their cells of origin.

Case Mrs. E. D. Transverse sections from this case are shown in figure 3. This patient had repeated injections of phenol in glycerol and silver nitrate and phenol in glycerol during the last seven months of her life. The sections illustrate a point mentioned in the previous case but shown more vividly here. This is the common finding that all the fibres of some bundles are degenerating, but in neighbouring bundles the degenerating fibres may be confined to one or more small areas. The Marchi section (fig. 3A) shows the degenerating myelin; the Haggqvist section (fig. 3B), from an adjoining block, shows the darkly stained areas of fibre loss and increased collagen.

Case Mrs. I. R. This patient had an injection of 2.5 per cent phenol in glycerol three months before death. The gross appearance of some of the sacral nerve roots after fixation is shown in figure 4. The arrows indicate the parts of the roots where there is thinning and separation of the bundles. Histological examination has confirmed that these are the areas of maximum destruction, although there is also destruction in other parts of the roots. In this patient it would seem most probable that the phenol in iophendylate dripped from root to root, as well as flowing along the length of the roots.

Spinal cord.

One of the most striking findings seen in all the cases is the marked degeneration of nerve fibres in the posterior columns. These fibres are large and myelinated. The origin of this degeneration will now be considered. It might be due to invasion by neoplasm of the posterior root ganglia, posterior roots or spinal cord, or it might be due to the injected phenol solution. Evidence of neoplastic invasion of a site likely to give rise to degeneration in the posterior columns was seen at postmorte in only five cases; but invasion by neoplasm could not be dismissed as a possible cause without further consideration. As only the cord and proximal parts of the roots were available in most cases, the presence or absence of neoplasm in the more peripheral parts of the roots could not be established.
Transverse sections of sacral cord and lumbosacral roots of patient who had repeated injections of phenol in glycerol and silver nitrate and phenol in glycerol during the last seven months of her life.

A. Marchi preparation showing distribution of degenerating myelinated fibres (×15).
B. Häggqvist preparation. The areas of dark staining are characterized by fibre loss and increased collagen (×33).
Fifth lumbar and upper three sacral roots from patient who had intrathecal injection of 2.5 per cent phenol in glycerol three months before death. Thinning and separation of the bundles indicated by arrows, which also indicate possible direction of flow of injected solution (×1.5).

FIG. 4

Diagrams showing sites of lesions which do and do not produce posterior column degeneration.

A

B

C

The site of the trauma to a nerve fibre determines the histological findings, as is well known. Figure 5 shows diagrammatically the possible sites of lesions, not involving the cord itself, which can cause degeneration in the posterior columns. If a lesion is distal to the posterior root ganglion, as in A, it is unusual to find degeneration in the posterior columns unless the lesion is very close to the ganglion. If the ganglion is partially involved, as in B, there is some degeneration in the posterior columns; and if the ganglion or posterior root is completely destroyed, as in C, then there is marked degeneration in the posterior column, in the distribution of the affected root. In this statement the term “a lesion” is taken as being equivalent to “destruction of nervous tissue”. When the lesion is in the form of a neoplastic growth the extent of the destruction may be considerably less than anticipated. The presence of tumour around the posterior root ganglia, in the root ganglia, and even invading the roots, cannot be taken as indicating that there will be, inevitably, degenerating fibres in the posterior columns. The number of nerve fibres degenerating, both in the roots and in the cord, as a result of destruction by invading neoplastic cells is often surprisingly
slight. Figure 6 shows the incidence and degree of posterior column degeneration in the control (i.e. uninjected) group of cases having malignant disease in the lower limb or pelvic organs, and the similar cases in which intrathecal injections of phenol solution had been carried out. Any degeneration of the fibres of the posterior columns in the control cases can be assumed to be due to neoplastic cells having invaded the posterior root ganglia or possibly the nerve roots. It can be seen that in this group of forty cases there is degeneration in the posterior columns in thirteen, an incidence of approximately one in three. In the sixteen cases treated by intrathecal injections in the lumbar region there is degeneration in the posterior columns in every case, that is sixteen in sixteen. On the basis of the incidence of posterior column degeneration in the control group the number of cases which might be expected to show degeneration due to malignant disease is five out of sixteen. This is in fact close to the actual proportion, four in sixteen, of the patients, treated by injections in the lumbar region, in whom invasion of posterior root ganglia and/or nerve roots had been seen at postmortem. It is therefore concluded that it is most improbable that the degeneration in all the other cases is due to invasion by neoplasm, and that it is more probable that it is due to the injections. There are certain features of the degeneration in both the injected and the control cases that support this conclusion. It can be seen from the control group that the degeneration in the posterior columns resulting solely from the neoplasm is seldom so marked as that seen in the injected group; total loss of posterior column fibres due to destruction by neoplastic invasion is rare; moreover, it is unusual to find in the posterior columns that two or more roots are affected, with sparing of the intervening roots, such as can be seen to have occurred among the cords from the injected cases.

The histological appearance of the actual degenerating fibres is often of value in deciding whether the changes are due to the injections, because when the nerve fibres are in that stage of degeneration that is consistent with the interval between the injection and death of the patient, it is reasonable to deduce that degeneration is, in part at least, due to the injection. This is illustrated in figure 7. In figure 7A, the injection was made three weeks before death. The Marchi preparation shows fibres in the swollen, beaded and early disrupting phase of degeneration. In figure 7B the injection was made two months before death. The fibres are mostly in the free, broken-up round "Marchi body" stage of degeneration with a smaller number of disrupting fibres and compound granular corpuscles. In figure 7C several injections were made in the period ten to twelve months before death. The black-staining products of myelin degeneration are mostly in compound granular corpuscles with comparatively few free Marchi bodies. In each figure the appearance of the products of degeneration is consistent with a lesion made at the time of the injection.
When this evidence is considered together, there appears to be little doubt that the intrathecal injections have caused degeneration of the posterior column fibres in every case, although in only some of the cases can it be concluded that the injections have caused all the degeneration.

The next point to consider is whether there is any evidence that the action of the phenol is ever on the spinal cord itself rather than on the roots or ganglia. In figure 8, a series of sections from one patient, Mrs. M. B., is shown. A number of posterior roots can be seen to be degenerating. The pattern of degeneration in the posterior columns conforms to the distribution of the fibres from posterior roots of different segments. If the degeneration came from the action of the injected solution directly on the surface of the cord, then the degenerating fibres would lie on the periphery of the posterior columns and not in the anatomical distribution of the posterior roots. Further, there is no degeneration on the periphery of other parts of this cord. It may therefore be concluded that in this case the cord itself was not damaged by the phenol. Further, in none of the cords has there been any border of peripheral degeneration nor has degeneration been confined to the periphery. It may therefore be concluded that the effect of the phenol is not due to its direct action on the spinal cord itself.

One patient with survival period of forty hours.

In one patient intrathecal therapy consisted of a single injection of silver nitrate and phenol in glycerol. This patient developed a marked meningeal reaction and died forty hours after the injection. Evidence of leptomeningitis was found at postmortem, being most intense in the posterior meninges, immediately caudal to the eighth cervical vertebra, where the injection had been given. This patient was the only one who died as the result of an intrathecal injection. It is to be noted that six other patients had an injection of the same solution and did not show the same reaction. In two of them the intrathecal injections were given at levels where the spinal cord is present. In one, phenol in glycerol was injected at the upper cervical level. In the other, three injections of phenol in iophendylate and one injection of silver nitrate in phenol in glycerol were given at the mid-thoracic level. Nothing distinguished the clinical history following the injections, nor the histological findings in these patients from the remaining patients in the series in whom the injections were given at levels caudal to the spinal cord. It is not possible to say why there was such a marked reaction to the injection in the patient reported above. It may be that there is an increased risk of reaction when injections are given at the lower cervical region, where the cord is large and the space between it and the vertebral canal is at its smallest, and that solutions containing silver nitrate tend to produce a more marked reaction. As this is a single case, however, no definite conclusions can be drawn from it.

**DISCUSSION AND CONCLUSIONS**

It has been established from the cats reported above and in another paper (Nathan, Sears and Smith, 1964) that solutions of 1–7.5 per cent phenol in iophendylate placed around one or two nerve roots within the subarachnoid space cause degeneration of nerve fibres; moreover this degeneration affects fibres of all sizes. Further, although most or all of the fibres comprising a rootlet may be destroyed by this solution, the continuity of the rootlet is not lost.

Degeneration of nerve fibres in the posterior roots and in the posterior columns of the spinal cord was a constant finding in the injected patients. It is concluded that this degeneration of fibres is due to the injected solutions and not to invasion by neoplasm, and further, that it results from the action of the solution on the nerve roots or ganglia, and not on the spinal cord itself.

The site of action of the injected solution was found to be along the length of the posterior nerve roots, between the posterior root ganglia and the spinal cord, and in the anterior roots in the same distribution but to a much smaller extent. Changes in ganglion cells have not been extensive, except when the peripheral nerves arising from the ganglion are involved in neoplastic tissue close to the ganglion. A marked reaction in the epidural tissues does occur especially in the region of the proximal pole of the ganglion.

The histological evidence shows that destruction of nerve fibres takes place wherever the phenol comes into contact with them. In most
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Fig. 7 (left)
Appearance of degenerating myelinated fibres in the posterior column and horn at different periods of survival after the injections. The figures on the right are enlargements of part of the middle field of the figures on the left (Marchi ×18; ×90).
A. Survival: 3 weeks. Fibres swollen, beaded and disrupting; there are many in the grey matter.
B. Survival: 2 months. Fibres mostly in free, round "Marchi body" stage of degeneration with some disrupting fibres and a few compound granular corpuscles. There is a considerable number in the grey matter.
C. Survival: 10–12 months. Products of myelin degeneration mostly in compound granular corpuscles with a few, free "Marchi bodies". There are a negligible number in the grey matter.

Fig. 8 (right)
Series of transverse sections from one patient to demonstrate pattern of degeneration (black) in posterior roots and columns after intrathecal injection of phenol in iophendylate (Marchi ×7). Note that the degeneration in posterior columns conforms to distribution of fibres from different posterior roots, and that there is no peripheral border of degeneration.
cases there is destruction of all the fibres of one or two rootlets and partial destruction of neighbouring rootlets. So far the impression has been gained that there is no selective destruction of fibres—those of different calibre all being involved in the lesion. Certainly all fibres are destroyed in each patch of main destruction. The possibility of selective damage of small fibres in the parts of the bundle adjoining these patches of destruction has been considered, but this was not found. Further work on this point is reported elsewhere (Nathan, Sears and Smith, 1964).

The conception of the passage of the injected solution based on the findings in this material is as follows. The injected solution tends to run along all the nerve roots with which it makes contact, spreading both centrally and peripherally, presumably owing to capillarity. As the solution leaves the needle it flows along any roots adjacent to the needle, and also may drop by gravity on to adjoining roots and on to the arachnoid membrane covering the spinal canal. Here it may also make contact with those roots which are approaching their intervertebral foramina, spreading along them. One might have expected that the solution would pass along the nerve roots, or along the surface of the spinal canal, to reach the posterior root ganglion and destroy neurones there. There is, however, little evidence of any local action of the solution on the ganglia, and the extent of fibre degeneration in the roots close to the ganglion does not exceed that in other parts of the roots. This is probably due to the anatomical relationship between the lumbosacral ganglia and their roots. Except for the last two or three sacral ganglia each ganglion lies deep in the intervertebral foramen. The posterior root, as it leaves the ganglion, lies deep in the intervertebral foramen. The anterior root, within a sleeve of dura mater measuring up to 14 mm in length. The pia-arachnoid covering the dura and nerve roots forms a cul-de-sac at the proximal pole of the ganglion and here it is increased in amount between the roots. This pocketing of the ganglion and the presence of the reduplicated pia-arachnoid probably tends to impede the flow of the injected solution to the ganglion itself. As the activity of the solution with respect to the nerve fibres appears on clinical grounds to occur mainly during the first 5 minutes after the injection, any slight delay in the initial flow of the solution is probably significant in determining its site of action. Further, even if the ganglionic cells were to come into contact with the injected solution during its destructive phase, it seems probable, judging from the limited extent of the lesion in most roots in relation to the total transverse area of the root, that only a few cells in the proximal pole of the ganglion would be destroyed.

When the clinical state is considered in relation to the histological findings, it is evident that the destruction of considerable numbers of nerve fibres of all sizes occurs with no, or almost no, loss of sensibility; moreover, this destruction of fibres of all sizes may stop the chronic severe pain.

Berry and Olszewski (1963), reporting briefly their findings in three patients who had had injections of a 5 per cent solution of phenol in glycerine, also did not find any evidence that small fibres are predominantly affected by the solution. In one of these patients they were unable to find any histological evidence of any effects of the injection in the tissue available for study. Baxter and Schacherl (1962) examined cats which had received single intrathecal injections of one of the following: 7.5 or 15 per cent phenol in glycerine; 7.5 or 15 per cent phenol in saline. These workers also did not find any selective damage of small nerve fibres. They did find vasculitis, proliferative arachnoiditis, and peripheral demyelination and occasional infarction of the lower part of the spinal cord. It must be noted that all the solutions used were stronger than those used in the present study; for it has been shown by Nathan and Sears (1960) that solutions of phenol in glycerol are more active than those in iophendylate. It is of interest that Baxter and Schacherl found the same but less extensive effects as after phenol solutions when ethyl alcohol or glycerine alone were injected. Stewart and Lourie (1963) also studied the destruction of nerve fibres in the roots of cats after subarachnoid injections of 10, 7.5 and 5 per cent phenol in Pantopaque (iophendylate). They found no evidence of selective destruction of certain nerve fibres.

It has already been noted that direct damage to the cord has not been seen in any case reported here. It is of interest, on the other hand, that in
a series of patients previously studied, who had received intrathecal alcohol for the relief of pain, there was, in most instances, a narrow peripheral ring of degeneration extending round all or most of the cord.

The histological evidence from the eighteen cases examined after intrathecal injections of phenol in iophendylate or glycerol for the relief of pain indicates that this method, when applied as described by Maher and others, is not likely to produce undesirable effects on the meninges or spinal cord. No histological differences were found in those cases in which silver nitrate was injected in addition to the phenol solution and those in which the phenol solutions alone were used. In the one case in which a single injection of silver nitrate and phenol in glycerol was given at the low cervical level, meningitis developed. No deductions regarding the detailed action of this injection could be made.

In all the cases studied here the intrathecal injections were given for the relief of pain, the concentration of phenol being in no instance stronger than 8 per cent. Stronger solutions are being used for the relief of spasticity (Nathan, 1959; Kelly and Gautier-Smith, 1959); the histological findings reported here cannot be assumed to be equally applicable to cases treated by the stronger solutions.

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The results reported here are only one aspect of a study done in conjunction with Dr. P. W. Nathan and Dr. T. A. Sears, and I am indebted to them for allowing me to utilize the experimental material. I want to thank all the physicians, surgeons and pathologists who generously helped. In particular I thank Professor W. Blackwood, Dr. D. Harriman, Dr. W. G. P. Mair and Dr. A. Maloney for their great help with necropsies and liberality with cases. Dr. E. A. Carmichael stimulated and advised throughout the study and I am most grateful to him. Miss Anne Ebbom and Miss Janet Small are responsible for preparing most of the sections and Mr. K. L. Frampton for the photography. My warmest thanks go to them and to the other technicians who have given their assistance.

REFERENCES


EXAMENS HISTOLOGIQUES APRES INJECTION INTRATHÉCALE DE SOLUTIONS DE PHENOL POUR COMBATTRE LA DOULEUR

SOMMAIRE

Le système nerveux de dix-neuf malades atteints d'affections cancéreuses et qui avaient reçu des injections intrathécales pour combattre la douleur a été examiné. Dix-huit malades avaient reçu une ou plusieurs injections de phénol dissous dans l'iophendylate ou dans le glycérol, chez six malades on avait pratiqué en outre des injections de nitrate d'argent et de phénol dans l'iophendylate ou dans le glycérol. Un seul malade avait reçu une seule injection de nitrate d'argent et de phénol dissous dans le glycérol. On a examiné d'autre part un matériau provenant de onze chats auxquels on avait appliqué du phénol dans l'iophendylate au niveau des racines nerveuses postérieures. Les résultats histologiques obtenus chez un de ces chats sont décrits dans le présent travail. On a examiné d'autre part une série de contrôle de moelles vertébrales de quarante malades cancéreux qui n'avaient pas reçu d'injections intrathécales et qui souffraient de cancers des organes pelviens ou des extrémités inférieures. Voici les principaux résultats de ces études: (1) Le phénol dans l'iophendylate ou le glycérol provoque une dégénérescence à la fois des grandes et des petites fibres nerveuses. (2) Le phénol agit sur les fibres au niveau des racines nerveuses et non pas sur les ganglions ou sur la moelle épiplète. (3) On a constaté une dégénérescence de la colonne postérieure dans tous les cas après injection. On en conclut qu'une partie au moins de cette dégénérescence est due dans les cas traités à l'injection. (4) On n'a trouvé, avec une seule exception, aucune réaction pathologique excessive attribuable aux solutions injectées. Chez un malade qui avait reçu une seule injection de nitrate d'argent avec du phénol glycérolisé on assistait au développement d'une méningite mortelle au bout de 40 heures.
Thus it is a little unexpected to find the suggestion that at the time of admission, written permission for operation and anaesthesia should be obtained. In England, at least, the patient signs that he agrees to an operation “the nature and effects of which have been explained to him”. It is perhaps not clear how much a nurse knows about the background of her work the more intelligent nurses require retention of reference to this particular section of the book. Their whole approach is essentially practical. The only section which the readers may find difficult to follow is that relating to the rectal administration of paraldehyde. It may be that the syllabus for the teaching of the patient to the nurse requires retention of reference to this particular section of the book. There is no mention of technics for teaching to nurses. Some feel that it is almost impossible to put too much into a textbook, and that the patient to the nurse requires retention of reference to this particular section of the book.

There are two schools of thought about what is appropriate for teaching to nurses. Some feel that it is impossible to put too much into a textbook, provided only that it is in a form which does not presuppose any previous knowledge of the subject and is sufficiently clearly and logically set out. Those who hold this view believe that the more a nurse knows about the background of her work the more intelligently she will do it. Others think that a nurse’s textbook should be brief, to the point, and concern matters only of immediate importance to the carrying out of her duties. The authors of this volume obviously belong to the second group, for they state clearly the problems involved in nurse’s handling of her patient and give precise instructions to her, often in the second person, about how she should discharge her duties.

Such a didactic approach to the matter allows little scope for the presentation of alternative points of view and the authors do, and are fully entitled to, state their own with emphasis. Inevitably, therefore, not everyone will agree with every statement made, and one or two are just a little surprising, unless it is that the law is slightly different in Scotland from what it is in England. Thus it is a little unexpected to find the suggestion that at the time of admission, written permission for operation and anaesthesia should be obtained. In England, at least, the patient signs that he agrees to an operation “the nature and effects of which have been explained to him”. It is perhaps not clear how a nurse admitting a patient could give the necessary explanation in every case. The authors, however, are to be congratulated on closing the gap which all too often exists between nursing procedures as they are described in textbooks and nursing procedures as carried out on the wards. Their whole approach is essentially practical. The only section which the readers may find difficult to follow is that relating to the rectal administration of paraldehyde. It may be that the syllabus for the teaching of nurses requires retention of reference to this particular section of the book. There is no mention of technics for teaching to nurses. Some feel that it is almost impossible to put too much into a textbook, provided only that it is in a form which does not presuppose any previous knowledge of the subject and is sufficiently clearly and logically set out. Those who hold this view believe that the more a nurse knows about the background of her work the more intelligently she will do it. Others think that a nurse’s textbook should be brief, to the point, and concern matters only of immediate importance to the carrying out of her duties. The authors of this volume obviously belong to the second group, for they state clearly the problems involved in nurse’s handling of her patient and give precise instructions to her, often in the second person, about how she should discharge her duties.

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