USE OF PHENOL IN RELIEF OF SPASTICITY

BY

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Maier (1955, 1957) drew attention to the remarkable effects of the intrathecal, subdural, and extradural injections of special solutions of phenol in the relief of pain, principally in cases of inoperable carcinoma. A surprising and interesting feature of these clinical experiments lay in the fact that very little additional neurological deficit was produced by these techniques, a phenomenon which Maier justifiably attributed to a selective action of the phenol upon pain fibres. Following up Maier's work, Nathan and Scott (1958) were able to show the relative safety of this method, particularly when using phenol in "myodil," though they commented on certain dangers they encountered in the use of a combination of silver nitrate and phenol. Brown (1958) also showed the value of solutions of phenol in glycerin and in myodil in the relief of pain, and alluded to the use of phenol in myodil for the amelioration of flexor and extensor spasms in three cases. Brown found no relief in two of these cases, and though there was relief in the third case the bladder became hypotonic. Maier (1955) had also alluded to the complication of retention occurring in his painful cases, particularly when he made his injections at a low vertebral level in order to relieve rectal pain, though his experience was that the retention cleared in three to four weeks.

The theoretical attractions of this method for the relief of spasticity and especially of the painful flexor and extensor spasms are obvious. Whatever one's views may be about the physiological mechanisms of postural tone, the clinical phenomena of spasticity must be attributable to a disturbance of the normal neural balance of the anterior horn cell. The pathological interruption of upper motor neurone pathways seemingly results in excessive activity of the afferent-efferent reflex arc. Pain transmission through the cord is still relatively unimpaired, and so one has the progression from spasticity to extensor and flexor spasms with associated pain. The functional defect in power in a case of spastic paraplegia is due in part to the interruption of upper motor neurone pathways and in part to the excess of stretch reflex activity in the lower motor neurones. Previous surgical attempts at anterior or posterior root section had stemmed from the acceptance of this theory but suffered from difficulties of technique and also from the fact that they resulted in a substantial increase in the existing neurological deficit.

With the advent of the knowledge that phenol solutions were capable of *selective* interference with pain transmission without noticeably adding to motor or other sensory deficit one naturally looked to this technique as a means of symptomatic relief for spasticity and especially for painful spasms. Consequently we began to carry out tentative experiments with

intrathecal phenol in patients for whom there seemed little other hope of clinical aid. It was only after some months, when we began to compare our experiences, that the details of the most effective and least dangerous technique finally emerged.

Technical Considerations

Solutions to be Used.—It soon became apparent to us that the combination of phenol in myodil was much less efficacious than that of phenol in glycerin. This was attributed partly to the fact that phenol is released more slowly from the myodil and partly to the fact that the glycerin-phenol mixture tends to be absorbed directly on to the neural roots, whereas the myodil tends to remain in globular emulsive form. As to the strength of the solution, we found that 5% phenol in glycerin was both safe and effective provided that careful attention was paid to the positioning of the patient. Weaker solutions appeared to produce effects of shorter duration, but in certain cases a 2% solution may be satisfactory, and we often use this in ambulant cases. The most suitable quantity to be injected at each session was again found by trial and error to be of the order of 1 ml., though quantities from 0.5 to 1.5 ml. have been given. The technique of preparation of the glycerin-phenol solution is as follows:

Phenol	...	...	...	5 g. (or 2 g.)
Glycerin	...	...	...	to 100 g.

The glycerin is dried for one hour at 120° C. and transferred to a dry stoppered flask. The phenol is added and the flask shaken until solution is complete. The solution is then filtered through filter paper and filled into dried 2-ml. ampoules. The use of rubber tubing and bungs at any stage of the process is undesirable, because rubber selectively absorbs phenol. "Polythene" tubing has been found satisfactory for the filling process. The ampoules are finally sealed and sterilized at 150° C. for one hour.

Anatomical Factors.—At first sight the anatomical considerations might appear to be simple and straightforward; for patients with excessive extensor thrust interruption of the L2/3 roots might reasonably be regarded as effective. Similarly, adductor spasm should theoretically respond to phenolization at these levels. If, on the other hand, flexor spasms predominate, chemical denervation at L4/5 and S1 seems the correct anatomical line of approach. These simple considerations, however, are complicated and conditioned by certain other factors. As hinted above, the principal danger lies in the affection of urinary bladder and sphincter action, with a resultant retention, and we have found that if phenolization reaches the cord itself (at L1) or descends to the sacral roots, then this particular complication is very likely to occur. Moreover, though one aims to restrict the phenolization to two or at the most three roots, there tends to be some spread of effect to segments above and below the point of insertion. We have therefore now come to the realization that the maximum safe efficiency results from injections either at L2/3 or L3/4 intervertebral spaces, though occasionally the L4/5 space has been used.

Technique

The technique of injection has now been evolved into a fairly rigid discipline. The patient is placed in the usual lateral position for lumbar puncture, and pillows are adjusted under the buttocks and trunk in such a way as to ensure that the appropriate intervertebral space is at the bottom of the putative watershed so

produced. Lumbar puncture is performed in the usual way in the space selected, an attempt being made, however, to direct the needle-point as far laterally as may be compatible with penetration of the theca. If, as the needle enters the theca, the patient complains of root paraesthesiae on the correct side the insertion is considered to be at its best. 0.2 ml. of a 5% solution of phenol in glycerin is injected slowly into the theca. (It is helpful to warm the solution to facilitate flow.) Patients are asked to comment on any sensation they may feel. Within 15 to 20 seconds they will usually say that they have a warm tingling in the region of the knee and thigh. Injection of a further 0.8 ml. of the solution over the space of 30 seconds then follows. If the initial paraesthesiae are in the buttock or ankle we advise discontinuance of the procedure, with a further attempt next day one space higher. Persistence of the injection in the face of such localization of the induced paraesthesiae almost invariably results in some bladder dysfunction. It will be found that within 60 seconds the injection has reduced tone in the leg.

Patients often complain of numbness and tingling, and for two to three hours there may be some motor affection, though in certain cases abolition of the spasticity may allow them to move a limb previously immobile. This motor deficit usually clears by the day after, and any objective sensory findings will similarly disappear. It is our practice to leave the patients for 15 minutes in the position in which the puncture is made. They are then allowed to lie on their backs with the head raised on two pillows for one hour. After that, full movement in or out of bed is permitted and indeed encouraged. The technique is repeated two days later on the opposite side, and we have given as many as six separate intrathecal injections to one patient in covering two intervertebral levels on each side.

Effect on Cerebrospinal Fluid

We had thought it likely that the introduction of phenol into the theca would result in a fairly brisk cellular reaction in the C.S.F. On no occasion, however, has there been any clinical sign of meningeal reaction, and serial examinations of the C.S.F. have shown that the only constant change is a rise in the protein content with excess of globulin and a minor alteration in the colloidal gold curve. These changes soon revert to normal, and may be regarded as of no clinical significance. On one occasion the cell content of the C.S.F. rose to 11 lymphocytes after the second injection, but the striking change lay in the protein elevation to 400 mg. in one case, this having reverted to levels of 60–120 mg. within the space of two to three weeks. These relatively minor changes in the C.S.F. have been rather surprising, but they indicate the relative blandness of phenol in glycerin when introduced into the theca.

Clinical Cases

We have now been able to observe the effect of treatment in 32 patients, some of whom received up to six separate injections, so that the actual number of intrathecal injections given is 75. From the diagnostic point of view the cases comprise the following:

Multiple sclerosis	..	..	..	..	21 cases
Parkinsonism	..	..	..	..	3 "
Syringomyelia	..	..	..	..	2 "
Hemiplegia of vascular origin	..	..	..	..	3 "
Spastic paraplegia—probably spinal type of disseminated sclerosis	..	..	..	..	2 "
Amyotrophic lateral sclerosis	..	..	..	..	1 case

From the functional point of view these cases could be reclassified in the following way. Six patients were mobile but had considerable spasticity in the lower limbs; the remainder were all chair- or bed-ridden. All but one were suffering from severe painful extensor or flexor spasms, the exception being one of the patients with syringomyelia whose leg was in a state of constant though painless extensor spasm.

Results of Treatment

It would be very gratifying to be able to record that this method of treatment has been an unqualified success, but unfortunately this is not the case. In general, however, the technique has proved of symptomatic value, and the following broad statements may be made about the results.

1. No mobile patient has been rendered completely immobile by the technique. In five cases mobility has been appreciably improved, with satisfactory reduction in the degree of spasticity and some improvement in function. In one of the mobile patients suffering from syringomyelia a severe degree of unilateral spasticity was converted to flaccidity of such degree that she was unable to walk for a period of two weeks, and now can walk only with great difficulty. In her case the total effect of function has been to her disadvantage, though from the academic point of view the spasticity has been completely abolished.

2. Rigidity of the lower limb due to Parkinsonism is significantly improved by phenolization, but tremor is unaffected.

3. It is the immobile patient suffering from painful flexor and/or extensor spasms who can most often be helped. The majority of the patients discussed here were suffering from multiple sclerosis and were bedridden. The main aim of treatment was to attempt to abolish painful spasms, and in every case this aim was achieved at least temporarily. In most cases the benefit has lasted for several months. It is thus possible to convert such patients from a painful life in bed to a chair-life of moderate comfort. Many of them were not able to sleep on account of the painful spasms and in particular they have derived great benefit from relief of this aspect of their problem. In two such cases—one of multiple sclerosis and one patient bed-ridden as a result of a vascular hemiplegia—return to walking was achieved after phenolization with the aid of orthopaedic manipulation of hamstring contractures and subsequent intensive physiotherapy. However, this conversion of an immobile patient to mobility is exceptionally rare. On the other hand, the abolition of the extreme spasticity may permit patients, still bed- or chair-ridden, to move and to be moved about in bed or in their chairs much more easily. The power which has been masked by the spasticity is unmasked by the process of phenolization, with obvious benefit. Almost universally the painful element of the spasm is removed or greatly diminished even if the motor factor is not improved.

4. As mentioned earlier, the major hazard concerns the disturbance of the urinary bladder and sphincter. In four of the cases treated, urinary control had already been lost before phenolization was carried out, and no change in sphincter status occurred. In four other cases the patients had already experienced some precipitancy and hesitancy of micturition, and in three of these retention developed after the first injection of the phenol. When this happened we immediately instituted tidal irrigation, and in two of the four cases the retention cleared within the space of three to four weeks. In the third case, after clearing the sphincter disorder has returned, and in the fourth case retention still persists after a period of seven weeks and seems likely to do so. Cystometrograms carried out in these cases indicate that the bladder is atonic. In this last case there is little doubt that the adverse effect upon the bladder was due to the fact that the phenol reached too low a level after injection. Maximum relaxation in this case was achieved

at the ankle, and after the first injection there was very little change in the degree of spasticity at the knee. This patient had acquired a pronounced scoliosis as a result of his neurological lesion, which has been developing over a period of 10 years, and it seems that, despite efforts to prevent the downward movement of the phenol solution, roots as low as S1 were affected. Later injections were carried out on this patient at a higher space with greater elevation of the buttocks and successful relief of the extreme spasticity in the leg.

Duration of Benefit

It is not yet possible to be definite about the expected duration of the reduction in spasticity, for the effects vary greatly from patient to patient. It is now over three years, however, since an intrathecal injection was carried out in an elderly patient who had developed a spastic flexion paralysis of the left leg as a result of a cerebrovascular (thrombotic) accident. Phenolization was carried out by one of us (R. M. M.) in April, 1956, using 1 ml. of phenol 5% in glycerin at a level of L 2/3. The pain and flexor spasms ceased immediately, and by the aid of physiotherapy the leg was gradually brought into extension. This patient is still ambulant three years later. Another female patient suffering from multiple sclerosis, which resulted in very frequent painful flexor spasms and made sleep almost impossible for her, received two injections, each of 1 ml. of intrathecal 5% phenol, in November, 1957. For six months pain and spasm were completely abolished, but then the spasms began to recur, though, curiously enough, without any associated pain. Two further injections at L 2/3 were carried out in January, 1959, with success, and when last seen (September, 1959), she was still completely relieved, though of course quite immobile.

At the other end of the time scale we have one patient in whom flexor spasms, seemingly abolished by intrathecal injection, returned within one week of treatment though again the pain element had been removed. We feel that in this particular patient the pathological process (multiple sclerosis) is still active and that this may be responsible for the return of spasticity on each occasion. In the main, however, it seems that appreciable benefit can be expected for an average of at least six to 12 months, though further observation may cause us to modify this opinion. Two patients (each suffering from active multiple sclerosis) have died within three months of the treatment being carried out, though in neither case did it appear that the procedure had accelerated the underlying disorder, and in both cases severe pain and flexor spasms were relieved. We have concluded, however, that it is probably inadvisable to administer this form of treatment to patients in whom the demyelinating process appears to be active.

Summary

The technique of intrathecal injection of the solution of phenol in glycerin is described, and the results of its administration to 31 patients are discussed. The manoeuvre is thought to be of circumscribed value in the relief of painful spasms in cases of spasticity. Careful positioning of the patient is required, and the possibility of resultant retention is emphasized. Care should be exercised in administering the treatment to patients who are still ambulant.

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ADDENDUM.—Since this article was submitted for publication two others have appeared on this subject, both in the *Lancet*, December 19, 1959. The first, by P. W. Nathan, deals with the use of 20% phenol solution in cases of spastic paraplegia in flexion, and the second, by R. E. Kelly and P. C. Gautier-Smith, with problems very similar to those discussed in the article.

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BIOASSAY OF THEOPHYLLINE PREPARATIONS USING HUMAN SUBJECTS

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The two chief disadvantages ascribed to theophylline are well known; it is poorly absorbed, probably because of low solubility, and it produces gastric irritation. To overcome these disadvantages, numerous theophylline salts and complexes have been introduced. In this investigation, using pure theophylline as a control, we have attempted to establish a hierarchy of clinical effectiveness among the various compounds by comparing the height and duration of blood levels which they produce in normal subjects and patients.

Method

Normal Subjects.—A group of 12 normal subjects, 21 to 35 years of age, selected at random, were used to study the blood levels of the preparations. Except for one subject (N. E. G.) all were males. At intervals of seven days, each subject received a single oral dose of each preparation listed in Table I in a dose equivalent to 400 mg. of theophylline.

Patients.—A group of 10 patients, 45 to 72 years of age, suffering from bronchial asthma, coronary artery disease, or primary hypertension each received a single

TABLE I.—Preparations Used to Obtain Comparative Blood Levels in Normal Subjects

Preparation	Theophylline Content (%)	Dosage Form
Aminophylline (theophylline ethylenediamine)	75-82	Capsule
Oxtriphylline (choline theophyllinate)	64.4	Coated tablet*
Theophylline	100	Capsule
Theophylline-choline	50	Coated tablet*
7-Hydroxyethyltheophylline	89	Capsule

* Commercial tablets were used.