INTRACTABLE PAIN *

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For clinical differentiation, pain may be classified as somatic or parietal, and sympathetic or visceral in origin. Greater attempts should be made to stress the points which differentiate these two types of pain.

The late Dr. J. B. Carnett spent twenty-five years observing and noting the facts connected with pain and tenderness. At the end of that time, he wrote his first paper on the subject. In the eight remaining years of his life, he stressed the differentiation of these two types of pain in sixteen papers.

At the time of his first publication he felt that he could differentiate between these two types of pain. He also mentioned many of the causes responsible for this incidence of somatic pain. He emphasized the fact that somatic or parietal pain was often misdiagnosed as visceral pain. Failure to differentiate the origin of pain resulted in needless and repeated operative failures. He demonstrated that many patients who had undergone repeated operations without relief of pain were suffering from pain which had its origin in the abdominal wall and not within the abdomen.

In the removal of causative factors, we attempted to eliminate all proved foci of infection. We corrected scoliosis and lordosis by heel lifts and Goldthwait exercises, and corrected metabolic and vitamin deficiency wherever possible. In addition, infiltration of the painful nerves and physical therapy were applied in our efforts to give relief.

We have learned that the distribution of tenderness which is associated with the pain is of greatest importance. Whether tenderness is absent or present is also an important point in the interpretation of symptoms.

Knowledge of methods to elicit the deep and superficial forms of skin tenderness is also essential. These details we have described in previous articles.

Pain which results from purely visceral stimuli is not associated with tenderness. However, when the visceral disease process irritates the parietal layers, localized and irregular areas of tenderness may be present, usually associated with muscle rigidity.

Clinically, the combination of segmental pain and tenderness does not appear to be initiated by stimuli from diseased abdominal viscera.

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The finding of a painful segment in which all of the cutaneous branches are hyperalgesic as compared to opposite normal side, with absence of rigidity or other clinical findings which denote visceral disease, indicates that the pain and tenderness are somatic in origin. In other words, we have a syndrome of segmental neuralgia which is *rarely initiated by any form of visceral stimuli;* although segmental neuralgia and visceral disease may coexist.

In 1931, Dr. B. Judovich prepared an aqueous solution derived from the pitcher plant, *Sarracenia purpurea,* and made the observation that it was of value in relieving pain of neuralgic origin. After several years of its clinical application by local infiltration, a summary of its action was published. At that time it was felt that its properties were due to the presence of amines. Judovich noted that the preparation had an action upon sensory nerves, relieving neuralgic pain without change in skin sensation, and having no effect upon the motor nerves. Controls with procaine, saline and water showed prolonged duration of relief in favor of the pitcher plant preparation. Tests of toxicity revealed that it was harmless. It caused no tissue coagulation or sclerosis. This action was unusual and difficult to substantiate, and routine pharmacologic tests had cast no light upon the problem.

This pitcher plant distillate has been used extensively for the relief of nerve pain by both of us in the Intercostal Neuralgia Clinic of the Graduate Hospital of the University of Pennsylvania, and also by others.

In no instance has there been any motor weakness following injection of peripheral nerves nor loss of touch, pressure, pinprick and temperature sensibility. In some instances one infiltration of the distillate is sufficient to provide permanent relief of pain even in cases of long duration.

In intercostal neuralgia, paravertebral injection of the root involved results in an immediate intensification of pain, followed during the subsequent thirty minutes by a gradual contraction of the hyperalgesic area in the dermatome supplied by the nerve, and in the majority of cases by complete relief of neuralgia. Because of the segmental overlap the effect of the distillate upon sensations other than neuralgia pain cannot be evaluated. However, if to relieve sciatic neuralgia the region of the sacro-sciatic foramen is infiltrated with pitcher plant distillate, there is again relief of neuralgic pain as well as of tenderness along the nerve trunk similar to the result obtained with infiltration of novocain, but in contrast to the action of novocain there is no numbness, no loss of sensibility, and no motor weakness.

In 1939, investigation was made by Drs. W. Stewart, J. Hughes and B. Judovich using the cathode ray oscillograph to determine the action of the pitcher plant upon the nerve impulse.

The ability of pitcher plant distillate to abolish neuralgic pain, which, like fascial pain, is aching, poorly localized, and frequently associated

with nausea and sweating, and at the same time to leave pinprick as well as other forms of sensibility unaffected, led us to inquire further into its physiological action and to attempt to determine its active principle.

The effect of pitcher plant distillate on the action potentials of the saphenous nerve of the cat was observed. The nerve was mounted in a nerve chamber in a gas mixture of 5 per cent carbon dioxide and 95 per cent oxygen. The temperature was maintained at 37.5 C. The nerve was so mounted that it could be bathed in the solution to be studied. The pitcher plant distillate was adjusted to a pH of 7.4. The action potentials were recorded on a cathode ray oscillograph.

After five minutes' immersion in pitcher plant distillate, the maximal A spike was somewhat reduced while the C fiber potentials were obliterated. The pitcher plant distillate was then fractionated and the various fractions tried for their effect on the saphenous nerve. It was found that the crystals obtained on concentration of the neutralized distillate likewise exerted a differential effect on the nerve potentials, depressing the C potentials more profoundly than the A Spike.

CHEMISTRY

It has been known since 1864 that the distillation of powdered pitcher plant root suspended in an alkaline solution yielded a volatile base. Bjorklund and Dragendorff came to the conclusion that the molecular weight of the base was not large, but they failed to determine its exact nature. We have reinvestigated the chemical nature of this volatile base.

A suspension was made of 500 Gm. of powdered pitcher plant root, *Sarracenia purpurea,* in 1200 cc. of distilled water and 400 cc. of 30 per cent sodium hydroxide. Steam was passed through the mixture until the last runnings of the distillate no longer gave a positive test for volatile base with litmus. The distillate was neutralized with hydrochloric acid and concentrated at reduced pressure. The solution was treated with a little charcoal, filtered and concentrated further until crystallization occurred. The crystals did not melt up to 320° and sublimed when heated in a small test tube over a free flame.

Elementary analysis of the substances gave the following values:

	Found: Cl, 64.6 per cent	Nitrogen 25.6 per cent
NH_4Cl	Calcd.: Cl, 66.3 per cent	Nitrogen 26.2 per cent

It, therefore, was evident that the crystalline compound isolated from the neutralized distillate was ammonium chloride. The crystalline substance yielded a flavianate, m.p. 289°. A 5 per cent solution of the isolated crystalline substance and that prepared from laboratory reagent ammonium chloride gave identical orange colored precipitates on treatment with an equal amount of Nessler's reagent, and white precipitates with 10 per cent phosphotungstic acid.

On titrating a definite amount of the distilled base, values were obtained indicating that 100 Gm. of pitcher root yielded 0.19 Gm. of ammonium hydroxide.

In another experiment, the alkaline distillate was neutralized with sulfuric acid and concentrated until crystallization occurred. The perfectly white crystals gave the following analysis:

Found:	N, 21.23	S, 23.92
Calcd.:	N, 21.21	S, 24.27

Therefore, the volatile constituent obtained by steam distillation from a mixture of powdered pitcher plant root and caustic alkali was essentially ammonium hydroxide; neutralization with hydrochloric or sulfuric acid formed the corresponding ammonium salt.

Varying concentrations of ammonium chloride in Ringer's solution of pH 7.4 were then tried for their effect on the saphenous potentials. Concentrations of over 1 per cent extinguished the A spike as well as the C potentials, while concentrations of less than 0.2 per cent diminished the C potentials only after prolonged soaking. Concentrations of between 0.2 per cent and 1 per cent resulted in greatest reduction of C fiber potentials accompanied by the least reduction of the A spike. Ammonium sulfate likewise had a similar effect. In fact, the active principle of the pitcher plant distillate which was used clinically and with which the depression of the C fiber potentials in the cat's saphenous nerve was first observed, was ammonium sulfate, as Judovich employed sulfuric acid to neutralize the distillate that he prepared, while Walti used hydrochloric acid. We are inclined to believe, therefore, that our results are due to the effect of the ammonium ion.

In order to determine whether a long standing depression of C fiber potentials could be reproduced in the experimental animal, a saphenous nerve infiltration of 0.65 per cent solution of ammonium chloride was made on the right and of 0.9 per cent solution of sodium chloride on the left.

On the side injected with ammonium chloride the C fiber potentials were extinguished. Compared to the side injected with sodium chloride the A potential was also reduced, but it was not as markedly effected as the C fiber potentials.

In man, perineural infiltration of 0.5 per cent to 1 per cent solutions of ammonium chloride produces the same effects as does the infiltration of pitcher plant extract. The immediate effect of the injection is an increased intensity of the pain which then subsides during the first thirty minutes after injection. The neuralgic pain is relieved, the zone of hyperesthesia contracts and disappears, and when injected around the sciatic nerve there results no weakness and the sensations of touch, pressure, pinprick, and temperature on the outer aspect of the leg are unimpaired.

These clinical observations lead us to believe that neuralgic pain and pinprick pain are mediated by separate fiber groups. Clark, Hughes and Gasser have demonstrated that unlocalizable pain is mediated by C fibers and that pinprick is mediated by fibers of large calibre. In man, perineural infiltration of the chloride and sulfate of ammonium in proper concentration exerts a selective depressing action on the type of pain, which, according to these investigators is carried by the C fibers.

While these experimental observations are not conclusive, nevertheless, supported by these clinical observations, they provide corollary evidence that unlocalizable pain, such as neuralgic and fascial pain, is mediated by C fibers and that more discretely localized pain, such as pinprick, is not mediated by C fibers.

CLINICAL EXPERIMENTS

As far as we can determine, from the clinical observations to date, injection of NH_4 salts or of pitcher plant does not affect the vasomotor components of the sympathetic ganglia or of the peripheral nerves, nor does it relieve pain of visceral origin. In eight cases of sciatic pain, injection at the sciatic notch with ammonium salts produced no change in surface temperature as determined by thermocouple readings before and after infiltration. Normal skin sensation and reflexes were preserved. The pain and hyperalgesia, however, disappeared. In these determinations, the needles were left in place twenty minutes, and 10 cc. of procaine hydrochloride 2 per cent solution was injected. Within two or three minutes, there was a rise in skin surface temperature of the extremities, numbness of the extremity and loss of the Achilles reflex, showing that the needles were correctly placed.

On two occasions the first and second lumbar sympathetic ganglia were injected in a patient with vascular occlusion of the lower extremities. There was no change in the skin surface temperature of the leg following infiltration of these points with the ammonium salts. The needles were left in place and at the end of twenty minutes 2 per cent procaine solution was injected. Within two minutes a definite rise in skin temperature was obtained.

In dealing with types of pain which should be transmitted through the sympathetics, we feel that the ammonium salts have no effect upon sympathetic pain, nor does the infiltration of sympathetic ganglia lessen pain of visceral origin.

These conclusions arise from data gathered by injection NH_4 salts both paravertebrally and intraspinally. In no case have we been able to control pain apparently of visceral origin by use of the ammonium salts. All cases responding to these injections were cases of pain of somatic origin associated with tenderness.

Since we have been able, on repeated occasions, to depress the small unmyelinated "C" fibers experimentally, and since by its clinical application we have been enabled to control severe pain in many patients,

it would appear that in those patients who did obtain relief of pain, it was by means of depressing these so-called "C" fibers. The sympathetic and their ganglia are made up largely of these small unmyelinated fibers. Yet the ammonium ion will relieve certain types of somatic pain and will not control visceral pain, or pain of sympathetic origin, nor will it affect the vasomotor components of either the sympathetic ganglia or the peripheral nerves. This suggests that some difference exists between the somatic and visceral unmyelinated fibers.

Since 1939, we have administered over 3000 injections of the ammonium salt preparations by paravertebral and local infiltration. Clinical results seem to justify the experimental evidence that the active principle of the pitcher plant is the ammonium ion.

The search for something new for the relief of severe pain has of course been mostly for the relief of the visceral or sympathetic type. Here we may have no known pathology as in tic douloureux, or we may have definite pathology such as malignant metastasis, or even cord tumors.

We are all familiar with the operative procedures of rhizotomy and chordotomy. Enthusiasts led us to believe that sympathectomies were going to be the answer to our long felt need, but we all know the disappointments which followed.

In the control of heart pain, ganglionectomies are still being done, but relief in most cases is being obtained by alcoholic injections of the stellate ganglion, or transplanting a new blood supply to the heart muscle itself.

INTRASPINAL ALCOHOL

Dogliotti, in 1931 described the technic of introducing ethyl alcohol into the subarchnoid space for the control of intractable pain.

In brief, it was based upon the fact that ethyl alcohol has a destructive action upon tissues, and that it has a low specific gravity (95 per cent—807) as compared to spinal fluid (1.007).

Therefore, the alcohol, when contacting the spinal fluid, floats to its uppermost level. Thus by adjusting the position of the patient, the alcohol can be directed to the desired area of the posterior roots in an effort to destroy the sensory fibers.

Since Dogliotti's report, observers have reported the use of intraspinal alcohol for many painful conditions, chiefly the intractable pain of malignancy.

In an autopsy study of four spinal cords of patients who had received intraspinal alcohol, Peyton reports that, "Sections through the spinal cord levels at which the alcohol was injected revealed a unilateral destruction of the posterior rootlets and of the lateral portion of the posteriorfuniculus. The posterior rootlet showed a patchy demyelinization. Some groups of fibers were completely destroyed, only a few fragmented sheaths and broken-up axones remaining. Other closely

adjacent bundles had undergone partial degeneration. A fairly distinct division between normal and abnormal tissue was present in most of the involved rootlet. Rarely did one observe diffuse involvement of a rootlet, but when it did occur, partially injured fibers were intermixed with intact as well as completely destroyed tissue."

The injured rootlets could be traced to their entrance into the homolateral dorsal funiculus. This portion of the cord, the fasciculus cuneatus, revealed changes quite similar to those of the injured rootlet.

Reports of satisfactory clinical results vary from 33 per cent to 100 per cent. That complications may occur is agreed upon by the observers reporting the larger series.

These complications have included bladder and bowel paralysis, motor involvement of the lower extremities, meningeal irritation with cloudy spinal fluid which subsides in several days, and even cranial nerve paralysis.

The general consensus of opinion appears to be that the use of intraspinal alcohol is a well worth while procedure, but that it should be reserved for incurable cases, and for patients who have severe pain which cannot be alleviated by other forms of therapy.

The treatment may be preceded by some form of sedation such as sodium amytal, 6 grains, or ⅙ grain morphine sulphate.

TECHNIC OF INJECTION

It is first necessary to determine which spinal segments are involved. This is done by interpretation of the distribution of the pain. This point, it seems, should be at the level of the spinal cord segment, and not at the points of emergence of the roots from the spine. Injecting at this latter location may account for some of the failures. The patient is placed in such a position that the posterior roots involved will be uppermost, the patient being in the lateral position. The lateral plane of the back is placed forward about 35 to 40 degrees which will aid in keeping the alcohol on a level with the posterior roots. The head and shoulders should be kept below the level of the area being treated. The spine at the area of injection may be arched in the lateral position by a pillow being placed under the patient. This will form a slight arc in the spine segment to be injected, the convexity being upward. Thus the area to be treated is on a plane higher than the rest of the spine.

A lumbar puncture is performed at the proper level. When free clear spinal fluid is obtained, a tuberculin syringe containing ½ cc. to 1 cc. of 95 per cent ethyl alcohol is connected to the needle and alcohol is injected slowly, taking about one minute to empty the syringe. The patient remains in position for one-half hour, after which he may be placed flat on his back. Alcohol used in these procedures should be filtered and autoclaved.

The injections may be accompanied by a burning sensation in the distribution of the area being contacted with the alcohol, followed by a

sense of warmth and numbness. This should, to some measure, give an idea whether or not the proper areas are being contacted. The degree and duration of pain following injection vary considerably. Relief of pain may be immediate, or it may be gradual, or not at all, depending with what accuracy the alcohol has been localized.

The patient should be kept flat on the back for several hours, and remain in bed for thirty-six hours to make sure that headache or other signs of meningeal irritation have not developed. If the pain is bilateral the other side may be repeated in a week.

Stern warns that more than 8 minims of absolute alcohol injected between L2 and L3 will invariably cause bladder complications, and that doses larger than 16 minims between L3 and L4 may cause rectal incontinence.

INTRASPINAL AMMONIUM SULPHATE

Due to the danger of loss of sphincter control when alcohol was injected into the spine, a drug having no effect on motor nerves was needed instead of alcohol. As we have reported, pitcher plant distillate or the ammonium ion relieved pain and had no effect on motor nerves. Therefore, Judovich started using it intraspinally instead of alcohol. The analysis includes 30 cases which were under his supervision and 20 cases from the observations of physicians who have employed this drug. These studies represent the adaption of pitcher plant (*Sarracenia purpurea*) derivatives and more specifically, ammonium sulfate, for the relief of pain. In the beginning, it was necessary to determine the degree of the patient's reaction, and the proper concentration of the solution. The first dose employed measured 10 mg. Ascending doses were administered intraspinally until a maximum of 500 mg. was reached. The optimum dosage appears to be from 200–400 mg. of ammonium sulfate in 5 cc. of distilled water. Five cc. of spinal fluid is withdrawn and discarded, and 5 cc. of ammonium sulfate solution is introduced into the spinal canal. This amount may be injected within a period of one minute.

TECHNIC OF INJECTION

The solution is hyperbaric or heavier than spinal fluid. The technic employed is the reverse of that used for intraspinal alcohol administration. Since this solution is heavier than spinal fluid, the injection is made in such fashion that the painful side is, therefore, turned down. If the pain is bilateral, the patient is placed flat on his back. Pain due to the injection usually lasts only several minutes, but, occasionally, it may persist for two hours. With pain in the lower half of the body, i.e., from the mid-thorax to the lower extremities, the head and shoulders should be kept slightly elevated. This is not done to prevent the solution from ascending to a high level, but to keep it at a point where it will

contact the area desired. The position of the patient should be maintained for half an hour following injection. The solution of ammonium sulfate causes no ill effect when injected at a high level, and the patient placed in the Trendelenburg position. In one of the cases, an injection was performed at the level of D10 (carcinoma of the breast, with metastases). Following the elevation of the foot of the bed, the patient described an ascending, burning sensation which reached the lips within a period of several minutes. Within two minutes, this disappeared and there was no residual effect noted. It should be clear that the level of injection should be high enough to take in the roots which supplied the painful areas. In the present series the highest injection was at the level of D5.

Intraspinal ammonium sulphate did not yield satisfactory results in the so-called "pre-metastatic" phase of malignancy. The complaints of burning, urgency, tenesmus and other pains of this period were not relieved.

At the time of injection, severe pain is experienced in the periphery supplied by the area bathed with this solution. This can be eliminated by preceding the injection with 50 mg. of procaine hydrochloride, which produces a mild spinal anesthesia.

Many of the patients developed nausea and vomiting following injections. Temporary motor effects were observed in several cases. Two cases had a temporary urinary incontinence lasting twenty-four to forty-eight hours, respectively. One patient had temporary bowel and bladder effect. Blood pressure readings were unaffected, but in a few patients there was a slight temporary rise.

*The solution of ammonium sulfate should be well diluted with spinal fluid while being injected. Since the optimal results develop from a concentration of 5–10 mg. per cubic centimeter, introduction of a solution of this strength is impractical because it is immediately diluted by the spinal fluid. Therefore, it is necessary to use a more concentrated solution, 50–70 mg. per cubic centimeter, and dilute it carefully and slowly with spinal fluid. The undue reactions we have seen appear to be due to insufficient dilution of the ammonium salts.**

In 2 patients who had prolonged motor effect, and in whom the fluid was properly diluted, we felt that metastatic infiltrations may have produced a block and prevented rapid dissemination of the solution.

It was noted in the group of failures that pain was not *associated with tenderness* of the sensory segments in nearly all instances. However, in the group of patients who developed metastases with root pain and tenderness, many excellent results were obtained. This observation has been further confirmed in patients with pain of known sym-

* Warning. The ammonium salts should not be injected intra-spinally unless a free flow of spinal fluid has been obtained. Concentrations in the spinal fluid are more than 15 mg. per cubic centimeter, may affect all fibers, causing loss of skin sensations, sphincter and motor paralysis. Free dilution and repeated barbotage are essential.

pathetic origin, i.e. coronary disease and vascular occlusion of the extremities.

Although our series of cases treated by intraspinal ammonium salts may be too small to be conclusive, the results paralleling those obtained in our cases of paravertebral injections, plus the experimental findings, encourage us in the belief that a contribution has been made toward the relief of intractable pain.

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For the information of anesthesiologists who are contemplating examination for fellowship in the American Society of Anesthetists, Inc. or who are training physicians for the specialty, the following questions have been employed in the past in *Pathology:*

1. Discuss cortical cell changes following prolonged asphyxia (hypoxia).
2. Discuss the choice of anesthetic drug for an appendectomy complicated by severe liver damage.
3. (*a*) List the principal pathological changes following aspiration pneumonia. (*b*) Outline the pathology of atelectasis. (*c*) What is the effect of alcohol used for therapeutic nerve block on a sensory nerve?
4. If chloroform is used to produce anesthesia, what tissue damage may result?