

# IRRITATING EFFECT OF IODIZED VEGETABLE OILS ON THE BRAIN AND SPINAL CORD WHEN DIVIDED INTO SMALL PARTICLES

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CERTAIN observations made on the unfavorable reaction to emulsions of iodized vegetable oils in the subarachnoid space of animals appear to be of fundamental importance to the neurologist and the neurosurgeon and are the basis of this report.

Some years ago, in a search for a limpid or an absorbable contrast medium for use in roentgenography of the fluid-bearing spaces of the spine and cranial cavity, it occurred to me that an emulsion of one of the commonly used iodized vegetable oils might serve the purpose, since these oils had been proved, by numerous clinical tests over many years, to be relatively free from irritating properties. Frazier and Glaser<sup>1</sup> had apparently already thought along the same line, since in 1928 they suggested the diagnostic use of iodized oil emulsions:

Another thought occurred to us: If an emulsion of the oil [iodized rapeseed oil] can be prepared which will diffuse rapidly with spinal fluid, such an emulsion, introduced into the ventricles, would be ideal for ventriculography.

While they carried out certain experiments with iodized rapeseed oil emulsion, apparently none was satisfactory because of its irritating property.

## EMULSIFIED MATERIALS

Emulsions were prepared from the three standard vegetable oils in common use: iodized oil U. S. P. (lipiodol<sup>®</sup>; an iodized poppyseed oil), chloriodized oil (iodochloral<sup>®</sup>; an iodized peanut oil) and iodized corn oil (my own preparation). It was hoped that the emulsion might be absorbed from the subarachnoid space if the particles were small enough—at least that it could be readily withdrawn through a spinal puncture needle when the diagnostic visualization had been completed. Emulsions of these three oils were made, much after the method of Frazer

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An abstract of this paper, with discussion, was published in a previous issue of the ARCHIVES (Irritating Effect of Iodized Vegetable Oils on the Brain and Spinal Cord, Arch. Neurol. & Psychiat. 62:523 [Oct.] 1948).

1. Frazier, C. H., and Glaser, M. A.: Iodized Rape-Seed Oil (Campiodol) for Cerebrospinal Visualization. J. A. M. A. 91:1609 (Nov. 24) 1928.

and Walsh,<sup>2</sup> by passing a mixture of 50 cc. of iodized oil, 50 cc. of isotonic sodium chloride solution and 5 Gm. of powdered acacia (the dispersing agent) through a high pressure emulsifier especially constructed for me for this purpose (fig. 1). It was possible by this method to produce an emulsion which was stable and which did not break down on being autoclaved. Most of the particles of oil measured less than 12 microns in diameter and thus might readily pass through the channels of exit from the subarachnoid space. There was no sign of free iodine in the completed emulsified materials. The final emulsion before injection was adjusted to a  $pH$  equal to that of spinal fluid.

Acacia was used as the emulsifying agent after it was determined that it had no ill effect on the tissues of the brain and spinal cord of dogs even in as high as a 6 per cent solution. Later, human and dog blood serums were used as the emulsifying materials, with no change in the experimental results. Incidentally, blood

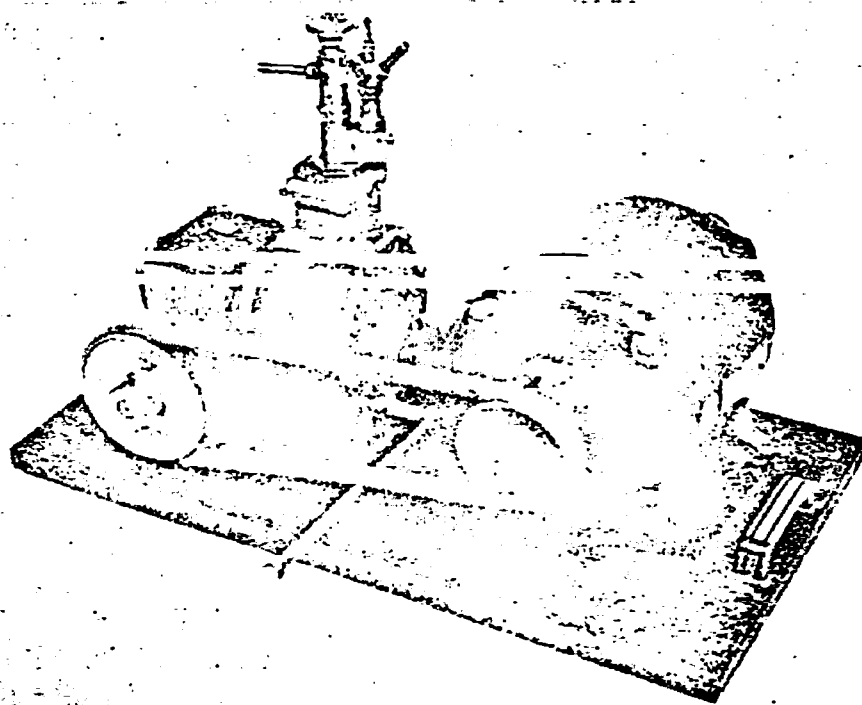


Fig. 1.—Pressure emulsifier used for preparing highly dispersed iodized oil emulsions.

serum was found to be an excellent dispersion agent. Controls were run by injecting iodized oil U. S. P., chloriodized oil and iodized corn oil in the same fashion as were the emulsions of these oils. Even in large quantities these oils produced no irritation. Dogs were used as the experimental animals.

#### EXPERIMENTAL PROCEDURE AND RESULTS

Approximately 0.5 cc. of iodized oil emulsion for each 10 pounds (4.5 Kg.) of body weight was injected into the spinal subarachnoid

2. Frazer, A. C., and Walsh, V. G.: An Apparatus for the Production of Finely Dispersed Emulsions, and the Rate of Digestion of Fat by Lipase in Relation to the Surface Area, *J. Physiol.* 78:467, 1933.

space, cisterna magna or ventricle of dogs, using each of the vegetable oils mentioned. The general result of the injection of the emulsion into each of these locations varied little except that the reaction was greatest near the site where the material was deposited. All the dogs became ill immediately after the injection, and most of them survived longer than 24 hours. Their illness increased, and most of them died within two weeks; those that lived for this period were so sick as to require being killed. The animals with injections in the spinal subarachnoid space frequently became paraplegic, but no part of the subarachnoid space escaped the devastating effect of the emulsion. Necropsy disclosed that there had been definite attempts to encapsulate pockets of the emulsion, and in the long-standing preparation the adhesions at the site of injections were extensive. The tissues in the spinal canal and at the base of the brain were matted together with inflammatory granulations and exudate. Abscess formation or extensive purulent exudate was not a feature of the reaction.

No rational explanation can be given for this reaction to the small particles of iodized oil. Each of the ingredients of the emulsion was adequately tested without any irritation being noted. Since human and dog serums used as the emulsifying agents gave the same results as acacia, it is assumed that the phenomenon must be a physical one, an irritation from the tiny particles of the oil. This poses the question of irritation from the fine particles left in the patient's spinal subarachnoid space when iodized oil has been injected for diagnostic purposes. The irritating effect of extremely small particles of iodized oil also suggests that any colloidal suspension may have a similar effect when injected subtheccally.

#### EFFECT OF ETHYL IODOPHENYLUNDECYLATE (PANTOPAQUE<sup>®</sup>) EMULSION IN THE CISTERNA MAGNA

Since the first of these experiments was completed, ethyl iodophenylundecylate has come into common use for spinal myelography and has justly displaced the other iodized oils, air and colloidal thorium dioxide (thorotrast<sup>®</sup>) as a contrast medium in the procedure. It is beyond doubt the most valuable material yet devised for this purpose, for the reason that it can be (and should be) entirely removed at the completion of the myelographic study.

In order to bring this study up to date, an emulsion of ethyl iodophenylundecylate was recently prepared in precisely the same manner as that described for the poppyseed, peanut and corn oils, except that the emulsion was made in a colloid mill. When it was injected into the cisterna magna of dogs in the same quantities as those used of the other oil emulsions, there was immediate death of the animal within 10 minutes. This effect, demonstrated in five dogs, indicates that an emulsion of

ethyl iodophenylundecylate is extremely toxic—even much more irritating than similar emulsions of the iodized oils previously used.

Inflammatory reactions in the spinal subarachnoid space following the injection of various iodized oils have been reported by many clinicians. It is seldom, however, that serious complications have developed after their use. Strangely, many of the unfavorable reactions have followed the attempted removal of the oil by opening the dura at the time of surgical exploration at the cauda equina or after the removal of a

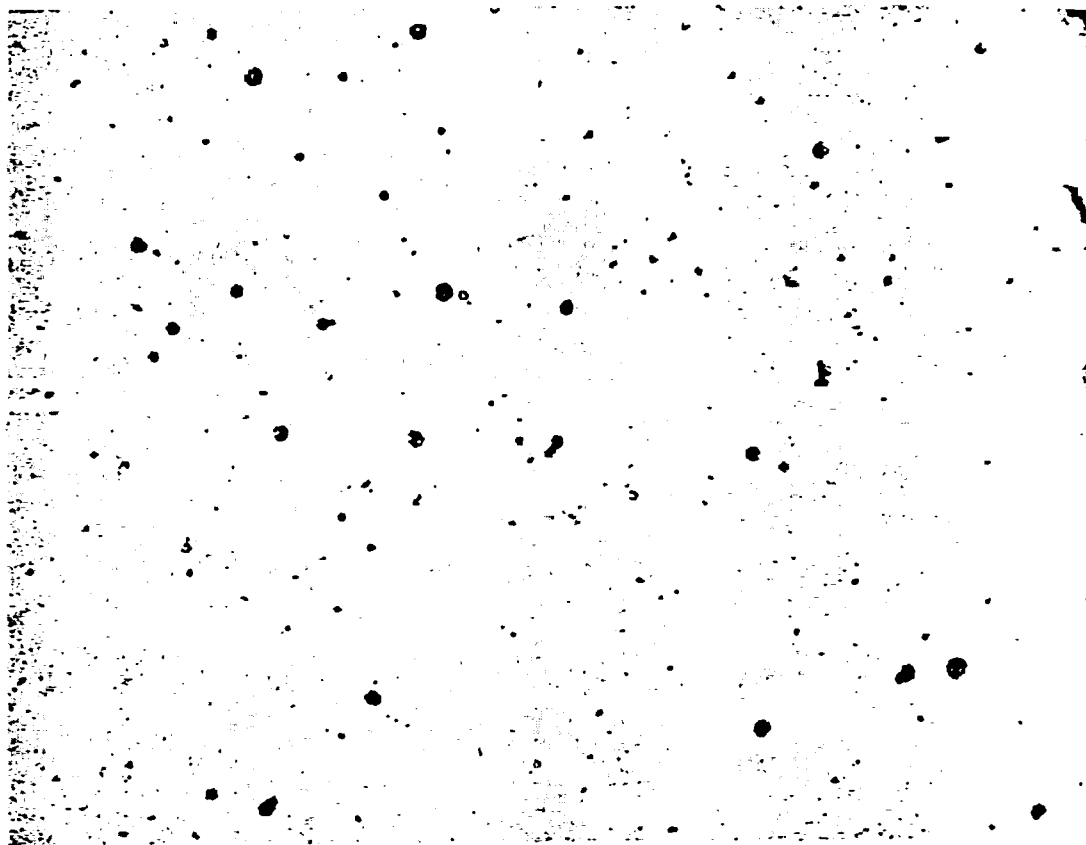


Fig. 2.—Dispersed particles of iodized oil (ethyl iodophenylundecylate; pantopaque<sup>®</sup>) three days after routine myelographic examination. The number shown here probably cause little or no harm. But if such colloidal particles are numerous, they can cause great irritation and incurable intrathecal adhesions.

tumor of the thoracic or lumbar region of the cord. Marcovich, Walker and Jessico,<sup>3</sup> in their careful study of this problem, stated:

... however, after the injection of iodized oil the dura mater is opened at operation, the oil commonly becomes rapidly encysted by proliferation of the arachnoid membrane. Pia-arachnoid reactions would therefore seem to be less likely if the dura is not opened.

3. Marcovich, A. W.; Walker, A. E., and Jessico, O. M.: The Immediate and Late Effects of the Intrathecal Injection of Iodized Oil, *J. A. M. A.* 116:2247 (May 17) 1941.

In the early days of intervertebral disk surgery it was not uncommon to find a matting, fibrous constriction of the cauda equina on reopening the dural canal. This state was undoubtedly caused by a combination of irritation from the dispersed iodized oil and the extensive transdural surgical approach of that time. Dispersion of the oil was encouraged by the attempt to mop out the oil in a bloody spinal fluid, which served as an ideal emulsifying medium. Extensive adhesions are no longer found when the ethyl iodophenylundecylate, now in common use, is completely removed prior to operation.

In view of the experiments with iodized oil emulsions described here, it would seem logical to assume that it is the tiny dispersed particles of the oil that cause the irritation. Blood serum is an effective emulsifying agent; therefore it should be reasoned that a mixture of iodized oil with bloody spinal fluid may result in dispersing the oil as tiny irritating droplets.

The lesson to be learned from this study is that iodized oils should be instilled into the subarachnoid space with due regard to their potential irritating property and, to prevent ill effects, they should be removed completely whenever possible, either before or immediately after the surgical procedure.

Jefferson Hospital (7).