SHORTLY after the introduction of air myelography for the demonstration of spinal tumors\textsuperscript{1,2,5,6,13,14} Sicard and Forestier described positive contrast myelography employing an iodized poppy-seed oil (Lipiodol).\textsuperscript{3,7–10,12} Because this procedure provided sharper contrast and easier interpretation, it initially received widespread interest. However, it was soon found to be associated frequently with meningeal irritation. In addition, the viscosity of Lipiodol led to occasional false filling-defects, and made its complete removal difficult. Because of these problems, the interest in Lipiodol myelography waned, and it was not often performed after 1950.

During the following ten years, neurosurgeons became aware of the disease process of protrusion of the intervertebral discs, and interest in myelography was again stimulated. A number of new contrast media were proposed, but most were discarded because of unpleasant side effects.\textsuperscript{12} In 1941, the relatively nonirritating iodine-containing oil, Pantopaque, was introduced.\textsuperscript{4,11,15} This oil, less viscid than Lipiodol, was found to outline better the finer structure of the spinal canal, and proved easier to remove. Since that time, no better contrast medium for myelography has been introduced.\textsuperscript{4}

The two papers reproduced below represent the two major steps in the development of present-day myelography.

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GENERAL METHOD OF RADIOLOGICAL EXPLORATION BY IODIZED OIL (LIPIODOL)*

By MESSRS. SICARD AND FORESTIER

For a long time it has been recognized that the preparation of iodized oil, the so-called Lipiodol,
has the capacity to stop X-rays. However, radiologists have pointed out this fact only as a matter of simple curiosity.

We have thought that this particular quality of Lipiodol could be applied usefully to the radiological study of the cavities of the body. The results obtained have confirmed our hypothesis.

Lipiodol results from the complete and total combination of iodine and poppy-seed oil (Lafay). (We owe Mr. Lafay thanks for the liberality with which he has made Lipiodol available to us, as well as for the determinations of iodine which he has been kind enough to make in patients subjected to this medication.) Iodine is found concealed in this combination. The product is transparent, keeps the coloring of the original oil, but appears of a great density, not supernatant, but falling to the bottom of the water. Under the influence of a long stay in the open air, it becomes blackish, "and in this case it is preferable not to inject it" (Lafay).

One cc. of iodized oil contains about 0.54 gm. of iodine. This oleo-iodine is tolerated remarkably by the tissues. We have sometimes injected it in a dose of 10–12 cc. in a single lumbar-muscle hypodermic injection without provoking more than a local reaction of a transitory type. It causes no redness of the skin, it leaves no hardened tissue, and out of several hundred injections we have noted neither abscess nor general or local incident, and no appreciable tendency to encystment or to nasellomone. The injections can be repeated with impunity, even daily, into muscular or cellular tissues, up to an aggregate amount of 80–100 cc. (we have not yet exceeded this figure) without provoking the least sign of intolerance. It can be injected intravenously (Rathery).

Furthermore, because of its heavy density, Lipiodol responds to gravity and passes readily into cavities or muscular interstices. It gives, either with impregnations at some distance removed from the original site of injection (fluid cavities and cerebrospinal fluid, for example) or with uninterrupted passages through tissues (muscles, epidural cellular tissue, etc.), movements of iodized oil of great interest to follow under radiological control. It remains visible radiologically for a long time in the tissues.

Thus, it is proved that Lipiodol combines all requisite conditions for exploring the cavities of the body without danger: great opacity to X-rays, absence of causticity and of toxicity, absolute tolerance, capacity for passage and prolonged visibility.

We first studied in a therapeutic and diagnostic respect the action of Lipiodol injected into the epidural cavity in patients with lumbar hyperesthesia, lumbar arthritis, or in those with lumboschialgia (see Sicard and Forestier. Exploration de la cavité épidurale par le lipiodol. Société de Neurologie, December 1921). We have, thus, obtained most convincing radiological illustrations.

The epidural cavity can be approached by the sacrococcygeal hiatus, as we have already demonstrated, or through the yellow ligaments all along the vertebral segments.

Sacrococcygeal injection of 2 cc. of Lipiodol permits, as soon as the day following injection, recognizing radiographically the epidural upward extension of the oleo-iodine to about the 5th lumbar vertebra. Tracks and spaces of iodized oil appear at the level of the sacral canals.

Epidural injection of Lipiodol made higher up by the lumbar method in the way of ordinary spinal puncture—rachicentesis—(but with a special trocar needle designed to avoid the opening of the dura mater and the egress of cerebrospinal fluid) permits seeing as early as a few hours after injection the lower extension of the oleo-iodine to the coccyx. If by a mechanical contrivance, such as placing blocks of wood under the feet of the bed, a kind of so-called static Trendelenburg position maintained for some ten hours is realized in the patient so injected, radiography will permit revealing, after this lapse of time, the high epidural localization of the iodized oil to the vicinity of the upper dorsal vertebrae, and that is realized by the tracks of iodized oil uninterrupted from the point of original departure of the injection.

It is understood that, according to the amount of Lipiodol injected, 2–6 cc. for example, and according to the point-of-reference epidural stages, the epidural cavity can be consulted methodically in its different segments when there is investigation, for instance, of a neoplastic diagnosis or one of Pott’s disease, indicated by pressure.

The epidural injections of iodized oil are painless and remain painless. The radiographic pictures become fixed almost definitely twenty-four hours after injection. The extension is halted from that time on and the resorption of the Lipiodol is so slowly produced that radiologic pictures taken in case of need, even several months later, are hardly altered. Patients with lumbar hyperesthesia, lumbar arthritis, and lumboschialgia benefit remarkably from the direct epidural therapy.

Injection of Lipiodol made no longer into the epidural cavity but into the cerebrospinal fluid after lumbar puncture is well tolerated, with this reservation, however, that the habituation of the subarachnoid sac to the foreign substance of iodized oil is accomplished only after a painful period of 2–3 days. It is necessary to warn about the appearance during this initial stage, 6–7 hours after injection, of symptoms of pain in the legs; namely, various paresthesias and formications, transitory reactions which are lessened markedly.
by the classic injection of morphine. Furthermore, these reactions are a function of the injected dose of iodized oil. They are at least reduced when the amount of the injection into the cerebrospinal fluid does not exceed 0.5 cc, but even in higher doses of 5-6 cc. the action of the sphincter has never been disturbed.

The Lipiodol in the subarachnoid sac obeys the effect of gravity. It collects, in the standing position, entirely at the bottom of the terminal sacral space, which it delineates as tapering into a point. In the dorsal or lateral decubitus, the Lipiodol extends into the stratum that spreads out along the posterior or lateral spinal tracts. It then forms a sheath around these tracts which detaches itself and is blackish, at radiography, over an extent of several centimeters. The Lipiodol in the cerebrospinal fluid persists for months without a tendency toward resorption. After this initial period of adaptation of 2-3 days, it is tolerated remarkably without provoking any trouble.

Injection of Lipiodol made into the lumbar subarachnoid space has given us very encouraging therapeutic results during tabes with shooting pains of the lower limbs and, likewise, during certain forms of syphilitic paraplegia.

We pass quickly over other more or less isolated attempts at injection of iodized oil into the cerebral arachnoid mater in general paralysis or into fistulous passages, articular collections of fluid, and urethral strictures. Our medical practice in this respect is still too limited.

On the other hand, we have pursued the study of this procedure applied to exploration of the broncho-pulmonary tree. . . Thus, iodized oil in organic combination of high concentration appears to us tolerated perfectly by the lung. One should be able to use it as a potent therapeutic agent because of its content in active principle and in the non-injurious form in which it is found. However, again, because of its opacity for X-rays, it permits carrying out on the living a radiological exploration of certain portions of the trachea and of the bronchi in a manner such as that used for the digestive passages.

It has seemed to us that, in its entirety, this method of new investigation by Lipiodol with respect to the cavities that up to now have remained unexplored radiologically, such as the epidual and the subarachnoid cavities, or the tracheobronchial-pulmonary tree, would be interesting to call to your attention and productive of practical deductions.

IODINATED ORGANIC COMPOUNDS AS CONTRAST MEDIA FOR RADIOGRAPHIC DIAGNOSIS

III. Experimental and Clinical Myelography with Ethyl Iodophenylundecylate (Pantopaque)*

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Ethyl iodophenylundecylate is one of a number of iodinated organic liquids that has been studied as a contrast medium for myelography. This new medium is a mixture of isoneric esters of which the principal constituent is probably that shown in the accompanying formula. It contains 30.5 per cent iodine and has a density of 1.263 at 20°C. The name Pantopaque was coined for this mixture to provide radiologists and clinicians with a convenient designation. The chemistry of this and of related diagnostic aids is discussed elsewhere (1, 2).

\[
\text{CH}_3 - \text{CH} - (\text{CH}_2)\text{COOC}_2\text{H}_4
\]

Ethyl iodophenylundecylate (provisional)

Prior to its clinical use, ethyl iodophenylundecylate was tested intrathecally in dogs in a series of comparative experiments against iodized poppy-seed oil. In these tests the new medium proved to be much easier to handle, produced discomfort of shorter duration, and in most of the animals was almost completely absorbed within a year. The clinical results have paralleled those obtained in animal experimentation.

As is shown in Table I, iodized poppy-seed oil is

| TABLE I |
| Coefficients of Viscosity of Myelographic Media |
| Medium | $\eta_{25^\circ}C$ | $\eta_{37.5^\circ}C$ |
| Ethyl iodophenylundecylate | 0.372 | 0.217 |
| Iodized poppy-seed oil | 8.06 | 3.76 |
| Ratio | 1:22 | 1:17 |

* Reprinted from Radiology, 1944, 43: 230-234, with the kind permission of The Radiological Society of North America, Inc.

1 These studies were aided by a grant from the Research Laboratories of the Eastman Kodak Company. They were presented before the Radiological Society of North America, at its Twenty-eighth Annual Meeting, Chicago, Ill., Nov. 30-Dec. 4, 1942, and submitted for publication in June 1944.

2 Pantopaque is a registered trade-mark.
that iodophenylundecylate micrographs, reduced there media sacrificed the animals. The experiments ally days. In weeks. With three mild clinically distress eight, but none palpable, as shown from injection. Because the new medium is so fluid, it is easily injected or removed with an 18- or 20-gauge needle and flows freely in the spinal canal immediately after injection. In dogs, however, where lumbar punctures are nearly impossible, and where the space relations of the canal are such that both media flow very slowly, practically none of the injected material can be removed.

Following intrathecal injection of 3 to 5 cc. of ethyl iodophenylundecylate in dogs, there is a period of slight fever, lasting one or two days, as is shown in Chart I. During this time the dogs are clinically well, but a fair proportion may exhibit mild distress when the head is bent. After two or three days, however, this symptom disappears. With iodized poppy-seed oil, on the other hand, there is no fever, but the period of distress when the head is bent may persist for ten to fourteen days. Sections taken from the spinal cords of dogs sacrificed at varying intervals show that both media are encysted after a lapse of about six weeks. The encystment is particularly noticeable in the cauda equina area and is not found generally throughout the cord. Typical sections showing the type of encystment that occurs are reproduced in Figure 1. As is evident from these photomicrographs, the size of the cysts with ethyl iodophenylundecylate is considerably less than that of those produced by iodized poppy-seed oil; this is probably referable to the greater viscosity of the poppy-seed oil. Cord sections taken at intervals from dogs injected intrathecally with ethyl iodophenylundecylate show that the physiological response about the cysts is essentially a foreign body reaction.

Acute toxicities for ethyl iodophenylundecylate were determined by intraperitoneal and intravenous injections. The LD 50 for intraperitoneal injections was found to be 4.6 gm./kilogram for mice and 19 gm./kilogram for rats. Control experiments with iodized poppy-seed oil showed no toxic effects with rats even when the medium was injected intraperitoneally at a level of 25 gm./kilogram. The injected ethyl iodophenylundecylate was completely absorbed in six weeks, however, while the iodized poppy-seed oil was not absorbed during the life of the experimental animal. The more rapid rate of absorption of the new medium may well be the sole cause of its relatively greater toxicity. Intravenous injections in dogs showed that ethyl iodophenylundecylate was without effect at a level of 0.5 gm./kilogram but was lethal at a level of 1.0 gm./kilogram. Emulsification with water containing small amounts of Igepon T (sodium oleylmethyltaurine) or of methyl cellulose reduced the toxicity considerably, and doses of 1.0 gm./kilogram were given intravenously to dogs with safety.

With the assurance from these experimental studies that the new medium was safe, it was first tested clinically on Nov. 23, 1940, by Drs. Paul Garvey and Nathaniel Jones in Case I, reported below. The absence of untoward developments
led to its use in 4 additional patients. The satisfactory outcome in these first few cases was followed by a wider use, until now the new medium has been tested in numerous clinics. The most extensive series of cases have been compiled by Dr. William P. Van Wagenen (Rochester, N.Y.), Dr. R. Glen Spurling (Louisville, Ky.), and Dr. William V. Cone (Montreal, Canada). From their experience it is evident that the best results are obtained if 3 to 5 c.c. of ethyl iodophenylundecylate are injected and later removed by the general procedure of Kubik and Hampton (3). In this way up to 90 per cent of the injected medium is easily removed and the small amount of residuum is completely absorbed within a few weeks.

3 As of November 1942.

Case Histories

Case I (Unit No. 171887): A 53-year-old male with complete paralysis from the waist down as the result of pressure on the dorsal cord from a dissecting aortic aneurysm was injected on Nov. 23, 1940, with 5 c.c. of ethyl iodophenylundecylate at L4 after removal of 8 c.c. of crystal-clear spinal fluid. Fluoroscopy showed a persistent constriction at L3 and L4, and also between L4 and L5. The patient experienced no reaction from the injection. Death occurred from a rupture of the aneurysm seventeen days later. A postmortem examination showed that the contrast medium was still mobile. Sections (Fig. 3) of the spinal cord showed a few polymorphonuclear cells around the nerve roots. There was no evidence of encystment in any portion of the cord.

Case II (Unit No. 173025): A 28-year-old white male with embryoma of the left testicle with bone and pul-

Fig. 2. Case II: Absorption of ethyl iodophenylundecylate in unusual case in which the nerve sheaths are filled with the medium. A. Immediately after injection. B. After three days. C. After forty days. D. After five months.
monary metastases was injected with 5 c.c. of ethyl iodophenylundecylate on Jan. 7, 1941. Films (Fig. 2) taken at intervals up to May 29, 1941, show a gradual absorption of over half of the injected contrast medium. Immediately after injection the Pantopaque became immobile as a result of filling the nerve sheaths, particularly the sheaths of the sciatic nerves. During the week immediately following the injection, the patient had a slight paresthesia in the lower leg. Otherwise there were no clinical symptoms. Death occurred at home and an autopsy was not obtained.

Case III (Unit No. 183121): A 29-year-old female with clinical symptoms of a ruptured nucleus pulposus was injected on Sept. 9, 1942, with 3 c.c. of ethyl iodophenylundecylate. A diagnosis of extra-medullary compression between L4 and L5 was somewhat equivocal. The contrast medium was removed and the patient was placed on fracture boards. On Sept. 21, 1942, 3 c.c. of Pantopaque was again injected, but fluoroscopy showed that some of it was extradural. For several days the patient experienced increased leg pain, especially after manipulation. Finally, on Sept. 28, 1942, a third examination was made with 3 c.c. of ethyl iodophenylundecylate and a positive diagnosis of a lesion at the disk space

Fig. 3. Case I: Section from the spinal cord seventeen days after injection of ethyl iodophenylundecylate. A few polymorphonuclear cells are seen.

Fig. 4. Case III: Reaction about probable site of extradural injection of ethyl iodophenylundecylate.
of L4 on the left side was obtained. A laminectomy was performed on Sept. 30. A section taken at the probable site of the extradural injection showed striated muscle and fibrous tissue. In the section reproduced in Figure 4 dense fibrous connective tissue is seen having a structure consistent with that of ligamentum flavum. In this tissue there is no evidence of any inflammatory reaction. Other portions of the section show striated muscle and areas of fairly loose connective tissue. Some of the striated muscle bundles appear to contain more than their normal number of nuclei, while others show considerable degenerative change. Instead of normal striated myofibrils the muscle sheaths contain a granular débris. This degeneration could be due to some local irritant, but similar changes are often seen without any known foreign matter in the vicinity. Several areas of the less dense connective tissue show infiltration by polymorphonuclear leukocytes in addition to many small round cells and a few larger monocytes. No definite droplets of contrast medium are seen, and there is no localized focal necrosis or abscess formation.

Summary

Ethyl iodophenylundecylate (Pantopaque), a new contrast medium for myelography, is more fluid and is therefore more easily injected and removed than previously described oil-type contrast media. In addition to these physical advantages, the medium is absorbed from the subarachnoid space with relative rapidity.

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