AN EXPERIMENTAL STUDY OF IODINATED COMPOUNDS

FOR INTRATHECAL USE

by

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INTRODUCTION

In this paper are reported the experimental studies with dogs and with other animals on a series of new liquid contrast media synthesized by Plati (1940) as a part of the Radiopaque Group program. These contrast media were all ethyl esters of iodinated aryl acids, and were designed to be absorbed at the site of injection, as well as to provide adequate contrast for radiographic diagnosis. From the esters investigated, ethyl isophenylundecylate has been deemed satisfactory for clinical use in myelography and is being employed for this purpose in a limited way. A second compound, ethyl-ω-(4-iodophenyl)-n-valerate, is in clinical use as a liquid contrast medium for purposes other than myelography.

The surge of interest in recent years in diagnosing intraspinal pathology, such as hypertrophied ligamentum flavum, ruptured intervertebral disk and spinal cord tumors, has led to the development of myelography. In order to outline the subarachnoid space, some material must be introduced to give contrast with surrounding structures. Air and various iodinated oils are now the standard contrast media, although the use of either has aroused much difference in opinion among the neurosurgeons, orthopedists and research workers. With air the radiographic contrast is poor; with iodized
oils the contrast is good but the oils cause reactions and are extremely slowly absorbed.

The ideal contrast medium should have the following characteristics:

1. Be non-toxic with little or no tissue reaction
2. Give good definition in radiographs
3. Be relatively stable to heat and to light
4. Be absorbed by the tissues with which it comes in contact
5. Be free-flowing

REVIEW OF THE LITERATURE

Since the advent of practical means of radiography, there have been many efforts to find suitable contrast media to outline body cavities. Since the soft parts within and surrounding the spinal canal are not dense to x-rays, there have been many attempts to outline the subarachnoid space. Air, oxygen, iodized poppy-seed oil, sodium salt of monoiodomethanesulfonic acid and thorotrust are four of the more widely used contrast media up to the present time. Dandy (1918) first proposed the use of air. Others since have employed the same technique, using oxygen alone or with nitrogen or helium.

Iodized poppy seed oil was introduced by Sicard and Foretlier (1922), and since has been widely used. The sodium salt of monoiodomethanesulfonic acid was used by Lindstrom and Arnell (1931)
but has not received wide acceptance. Beck and Warren (unpublished data), using the sodium salt of monomethoxyethanesulfonic acid and weak solutions of potassium iodide intrathecally, found a uniformly severe reaction usually followed by death. Hadefici and Miller (1932) published their studies on the use of thoroutrast in the subarachnoid space, but due to its radioactivity it is not accepted for this purpose.

Air and oxygen are the most widely used gas contrast media for intrathecal injection at present because they are less irritating than a fluid substance and are readily absorbed, leaving no irritating substance behind (Van Wagenen, 1934). However, the main difficulty with a gas for a contrast medium is that except in experienced hands, visualization of defects is difficult and not so accurate (Hampton, 1940) as with a fluid radiopaque medium, but it has a definite place as a diagnostic aid (Camp, 1940) mainly for encephalography.

Iodinated poppy seed oil, prepared by LeFay of Paris in 1901 and first used by Sicard and Foretstier (1921) as a radiopaque medium to outline the epidural space, was soon after used in the subarachnoid space. It is interesting that iodized poppy seed oil has been used in practically every cavity and sinus in the body for roentgenologic exploration. Halton (1925 and 1926) is responsible for development of its use in chest roentgenography. Sicard and
Forestier (1932), along with numerous others, have reviewed its usefulness in demonstrating intraspinal lesions. The use of iodized oil in roentgenography is well reviewed by Ruben (1926) and Randall (1937). In the male, for visualization of the seminal vesicles, urethra, and bladder, Sicard and Forestier (1926) have well summarized the usefulness of iodized oil. Froetz (1926) and Ernus (1937) have reported on the value of a contrast medium such as an iodized oil for roentgenography of the paranasal sinuses.

The work of Rosi (1936) and Doubilet (1937) has pointed out the usefulness of iodized poppy seed oil in roentgenography of sinuses and fistula tracts. Sicard and Forestier (1932) have published their attitude toward the use of iodized poppy seed oil, stating technique of injection, and contraindications. Sicard stated that iodized poppy seed oil should only be used as a diagnostic aid; no more than 5 cc. should be used for intrathecal injection; this oil should never be used where a local or general inflammatory disease of the meninges, is suspected. The Council of Pharmacy and Chemistry of the American Medical Association have also published a report in 1932 that adopts a more conservative attitude and discourages the use of any foreign body unless there is no other means of establishing an accurate diagnosis.

Since the advent of the use of iodized poppy seed oil in 1921, there has been a marked increase in the use of this material.
in the spinal canal. In the face of this increase, one is surprised, first, not to find more experimental work on the use of this iodized oil, secondly, not to find more pathological studies of human nervous tissue after this material has been used, and most surprising of all, to find very few early experimental studies before this foreign body was introduced into the subarachnoid space of humans. Sargent (1923), working in England, reported favorably on a small series of cases using iodized poppy seed oil in the subarachnoid space in humans.

In this country one of the earliest experimental studies is that of Ayer and Hixter (1924). The authors injected 1.0 to 1.5 cc. of iodized oil cisternally into six cats. They found the material to be impervious to x-rays, every droplet of oil being discrete and in no way to be confused with normal or pathological tissue. The oil diffused slowly throughout the cerebrospinal system, and there was no evidence of absorption. Spinal fluid counts were found as high as 4,420 on the third day after injection. The cats exhibited evidence of meningeal reaction lasting one, two, or three days. One cat died immediately after injection without evidence of injury to the brain at autopsy. No other pathological studies were reported. Sicard's comment on this work was that Ayer and Hixter used too much oil for the weight of the animal as compared with humans, the results, therefore, being in no way indicative of the
true reaction.

Klose and Paiper (1925) injected varying amounts of iodized poppy seed oil into the subarachnoid space of seventeen rabbits. Their mortality was 47 per cent. Objectively, their main findings in those rabbits were those of headache and root pain lasting one to four weeks. After these symptoms disappeared, the rabbits seemed to have completely recovered and remained well for two years. However, at autopsy, definite pathological findings were made. On removal of the cord and brain, the droplets of oil were adherent to the meninges and cyst formation was observed histologically. In the ganglion cells the Nissi granules were clubbed and definitely reduced in number. The cells themselves were pale and had lost their definite outline. Necrosis of the tissue adjacent to the spinal canal was also observed. These changes, Klose and Paiper believe, are due to mechanical pressure of the oil globules directly on the grey matter and indirectly on the white matter. Only slight disappearance of the material was noted.

An American observed, Maclaire (1925), reported one case of kyphotic cord injury in which iodinated poppy seed oil had been introduced into the subarachnoid space and caused thickening and adhesions of the leptomeninges with cysts of the arachnoid containing the oil around the old injury. The author concluded that this radiopaque medium increased nervous tissue and leptomeningeal damage and was irritating and, therefore, should be used only as a
last resort when laminectomy is contemplated. Sicard (1926) defended the use of the iodized oil in this case by stating that Maclaire did not observe the precautions and contraindications laid down for the use of the iodinated oil.

Lindblom (1926), of Sweden, reported on the effect of iodized poppy seed oil on the meninges. The compound was injected into the subarachnoid space of seven rabbits. One rabbit died of severe meningitis in 2 days. Six survived up to four months, exhibiting varying degrees of meningeal reaction for two to three weeks. Cord sections showed an acute leptomenigitis characterized by leucocytic invasion of the meninges around the oil droplets. No bacteria were found. Two months after the injection no histological changes could be demonstrated, even though large amounts of the oil were still present. In the same article, Lindblom reported three human cases. all showed evidence of meningeal irritation for 2 to 6 days with spinal fluid cells counts up to 1000/cu. mm., accompanied by nausea, vomiting and temperatures up to 39°C.

In the same year Ebaugh and Molla (1926) reported a series of 13 clinical cases with the iodized oil injected cisternally. They found a transient aseptic meningitis lasting a day or two. Four patients showed a definite rise in the spinal fluid cell count. Four exhibited leg pain lasting 3 to 4 days. Three had fevers ranging up to 101°F, lasting 4 days. One complained of nausea and vomiting.
for 2 days. All but 3 of the patients used in this study had central nervous system pathology: 5 paralytics, 3 multiple sclerotics, 2 degenerative neurologic lesions, and 3 with low back pain. All had an increase in cells of the spinal fluid before introduction. Other than the observation of the initial symptoms, no further studies were made on these patients.

Also in 1926 Sharpe and Peterson (1926) reported three cases in which iodinated poppy seed oil caused adverse symptoms. Two of their patients were suffering from degenerative nervous disorders. All 3 patients showed initial inflammatory reaction following the introduction of the iodized oil as evidenced by an elevation of cells in the cerebrospinal fluid. All suffered from root pain with the oil visualized at the root level. The oil, after 15 months, became fixed and would not move, regardless of the patient’s position. This was taken as evidence of encystment.

Two articles written by Sicard and Forestier in 1926 were interesting. One outlined the various ways iodized poppy seed oil could be used as a diagnostic aid. In the other, the authors stated that the oil did not act as a foreign body. If subjects are chosen correctly and proper technique employed, there is little danger to the patient. Sicard has followed patients for 4 years who suffered from no irritating effects of the oil. At post mortem he found the
oil fired by a light arachnoid network made up of mononuclears and phagocytes, but no true cysts.

Wolfeohn and Morrisscey (1927) reported two patients with cord tumors who suffered from an acute meningitis, and at operation definite inflammatory changes and cyst formation with iodized oil present were found around the tumors.

Globus and Strauss (1929) analyzed 61 cases studied by them, 25 of which had had the oil introduced two years before. In only one case were symptoms of increased root pain noted. The rest had uneventful recoveries. They concluded the iodinated poppy seed oil is remarkably free from untoward reactions, well tolerated, and of great diagnostic assistance. No spinal fluid cell counts were reported. Drs. Stockey, Spiller and Ayer, in discussing the paper by Strauss, pointed out that in their experience they had seen more evidence of irritation than the authors reported.

In the same year, Craig (1929) reviewed ten cases, upon iodized poppy seed oil had been used. He found definite signs of irritative meningitis in 4 cases. There was rise in spinal fluid cell count up to 26 per cu. mm., remaining at 143 per cu. mm. on the 25th day. Another case suffered from increased root pain over 1 month. In the third and fourth cases at operation the iodized oil was found encysted in the leptomeninges with evidence of localized inflammation around the oil.
Doughty (1929) also reported on the intraspinal effect of iodized poppy seed oil in three cases. He found no other difficulty than a transient rise in temperature to 100° F. in all of the cases. At operation 7 days later, no adhesions were found.

Davis, etc (1930), reported an experimental study on 10 dogs, injecting iodinated poppy seed oil into the subarachnoid space. After an artificial block had been produced by a laminectomy and the placement of a rubber dam in the epidural space, 1.5 cc. of iodized poppy seed oil was injected cisternally. Of the 10 dogs, 1 died in 3 days with severe meningitis. The rest survived and were sacrificed at varying periods up to 252 days. One dog developed a spasticity of a hind leg that lasted 6 months. In all but 2 dogs there developed a general malaise and anorexia that lasted up to 2 days. No mention was made of stiffness of the neck. After this initial period, the dogs quickly returned to normal.

At autopsy, definite pathological changes were found. There was a thickening and infiltration of the leptomeninges by round cells, macrophages, and a few plasma cells. Small globules of oil had become encysted at the site of the reaction. As was found by Kloss and Pieper (1925), Davis found that there were also degenerative changes in the anterior cord. The findings were mainly in the anterior horn cells. They were diminished in number and size, took stain poorly.
and the blood vessels supplying the uterine horns were thrombosed. Central experiments were done but not reported. Davis concluded that iodinated poppy seed oil is irritative and causes destruction to nervous tissue.

Braakins and Propper (1931), working on dogs, injected iodized poppy seed oil into the spinal canal of 8 dogs, and into the cord itself in 2 dogs. They found no sensory or motor disturbance. The dogs all survived and were killed at periods varying from 1 to 3 months. At autopsy in the 8 dogs injected cisternally, there were adhesions around the oil droplets with cyst formation, the walls of which were made up of fibrous tissue with round cell infiltration. These are the pseudogranulomata or fatty granulomata described by Lindblom (1931).

Lindblom (1931) reported research on the Effect of Various Iodized Oils on the Meninges. He found that animal oil such as cod liver oil had a very irritating effect. Uniodinated vegetable oils, such as soy, sesame, almond, linseed, and poppy, were much less irritating, the degree of irritation being directly related to acidity (soy bean oil has the lowest acidity; unrefined poppy seed oil the highest acidity). Iodination increased the irritative qualities slightly. Impurities were the main cause of irritation, free fatty acid, iodid fatty acid, and occasionally hydrogen iodide.

Contrary to earlier results obtained (Lindblom, 1926), he found
that iodinated poppy seed oil in the subarachnoid space of rabbits caused the development of fatty granulomata consisting mainly of phagocytes and surrounded by connective tissue. The nervous tissue was not studied.

Sicard and Perastiur (1932) surveyed the use of iodinated poppy seed oil in all conditions and again reiterated that, where iodized poppy seed oil had caused marked clinical reaction, the necessary precautions and contraindications for its use had not been observed. The few animal experiments performed by others were not to be misinterpreted as characteristic of human reaction.

Coggeshall and von Storch (1934) stated the following objections to iodized oils: First, irritation due to a foreign body in the subarachnoid space was found; second, the absorption was slow measured in years; third, false defects may occur due to the viscosity of the oil. These workers proposed wider use of air for a contrast medium to avoid the above difficulties.

Two years later Hampton and Robinson (1936) reported 100 cases in which 2 cc. of iodized poppy seed oil was injected into the subarachnoid space, and 75 in which 5 cc. was injected. They found an absence of any permanent sensory reaction. However, a definite reaction lasting several days was observed. This was characterized by a moderately elevated spinal fluid cell count, change in color
of the spinal fluid with an increase in protein, slight rise in
temperature, headache, and back pain. Since these findings
returned to normal gradually and since iodized oil offered a
definite aid in diagnosis, especially in rupture of the disk of
the spinal cord, Hampton and Robinson believed the use of iodized
oil was justified.

Globus (1937) reviewed 135 cases in which iodized poppy seed
oil was introduced into the subarachnoid space. In only two
cases did he find severe reactions immediately after injection.
One suffered a vasomotor reaction with recovery in several minutes.
This was attributed to the effect of the cisternal puncture. The
other case suffered a protracted period of pain along the spine,
in both shoulders. In a few instances there were mild transient head-
aches and slight elevation in temperature (about 1° F.). Sixty-five
of the 135 patients returned for reexamination several months to
several years after the injection of the iodized oil. One case
showed evidence of the oil in the subarachnoid space for 10 years.
Only one of the 65 had any symptoms. This patient had accentuation
of back pain. Thirty-four cases were x-rayed. There was no appre-
ciable reduction in the amount of iodized oil. On tilting the
patients, the oil was found to move. Three patients died in the
hospital, and no histologic evidence of leptomenigitis was found.
Therefore, Globus concluded that iodized poppy seed oil may be
regarded as a useful diagnostic procedure when used with established
methods of neurological examination.

Lyngehem (1938) reviewed 3,609 cases in which air or iodized poppy
seed oil had been used in the subarachnoid space. The 123 injected
with iodized oil suffered from more undesirable reactions than those
injected with air.

Netter and Leaks (1938) stated that numerous untoward re-
actions following the introduction of iodized poppy seed oil have
been reported. For this reason, the use should be carefully con-
trolled. If this oil is used, every effort should be made to remove
it at operation.

Brienen (1939), developed a technique for removal of iodized
oil from the subarachnoid space. He developed this technique in
an effort to avoid the meningeal reaction that this oil produces.
Brienen's technique is similar to that of Dr. Ascan at the Mayo
Clinic. Under anesthesia, the patient in the sitting position, an
incision was made over the second sacral vertebral segment, the
spine removed, and a hole 1 cm. in diameter drilled, uncovering
the subdural sac. The dura and arachnoid were incised and the oil
which had settled to the subdural sac flowed out. The dura, muscle,
and skin were then closed. Brienen acknowledged that Luherini (1936)
was the first to use this type of procedure.
Within the past few months, Kubik and Hampton (1941) have reported an excellent procedure for removing iodized oil from the subarachnoid space by low lumbar tap. In thirty cases they have had excellent results, removing 90 per cent or more of the radiopaque medium.

Brown and Carr (1941) reported an autopsy on a case 6 months after injection of iodized poppy seed oil. Oil was found enmeshed in old adhesions. The dura was thickened. There were fibrous adhesions running from the cord throughout the leptomeninges to the dura. The fibrous adhesions were infiltrated with lymphocytes. Brown and Carr concluded that the danger in using iodinated poppy seed oil must be realized, and, while the oil is a valuable diagnostic aid, it must not be used indiscriminately.

Garland (1940) summarized the clinical and pathological reactions. Immediately after lumbar, subarachnoid injection, there may be low back pain, headaches, and mild fever. These "post lumbar tap" symptoms subside in 3 to 5 days. In a small percentage of cases low back pain may persist for several months. The immediate reaction of the nervous system is an increased cell count in the spinal fluid and a hyperemia of the leptomeninges about the oil. The late pathological changes are fibroblastic proliferation with small round cell infiltration around the small oil droplets. These small cysts containing the oil were called pseudo or fatty granulomas. These
granulomata were small and have been mistaken for miliary tubercules at first glance. Much of the oil remained in large lakes and remained movable in the subarachnoid space. No secondary effect on neural tissue was reported by Garland. He concluded that iodized poppy seed oil has been of great diagnostic aid and that, until a better medium is found, its use is justified.

Hampton (1940) pointed out the usefulness of iodized poppy seed oil in diagnosing posterior protrusion of an intervertebral disc. Of 133 cases in which positive diagnoses were made, all but nine were proved at operation— an accuracy of 93 per cent. Even though air myelography had an accuracy of 50 per cent, air should be used first to avoid the questionable ill effects of iodized oil in half the patients Hampton reported. It was also pointed out in this article that iodized oil is a foreign body and remains for many years. Therefore, the patient should be suffering from a disabling disease that warrants the employment of a major surgical procedure. Of more than 200 cases in which iodized oil was injected into the subarachnoid space, only 4 have had persistent symptoms. Two complained of headaches, one of dorsal root pain, and one of sciogodynia.

Hampton also advised that iodized oil ought not to be introduced until at least a week after a lumbar puncture; if air myelography had been employed to wait until the air had disappeared. He found, as many others have, that the reaction of patients was
variable, some with no symptoms, some with fairly severe transient symptoms, and a very few with severe persistent symptoms. This, he felt, may be due to variations in the oil itself. Only fresh, practically colorless oil should be used.

In summary there is adequate evidence in the literature to show that in animals, iodized poppy seed oil produces a definite pathological change in the leptomeninges. Clinically, however, the animals may show little or no evidence of the reaction that is taking place. The evaluation of the reaction of humans to iodized poppy seed oil is difficult for the following reasons: many of the injections were done on patients suffering from degenerative nervous diseases; observations made at operations could not be entirely attributed to the effect of the iodized oil; lastly, very few complete pathological studies have been made on the central nervous system following the use of iodized poppy seed oil. Thus a review of the literature shows that there is still much doubt as to the effect of iodized poppy seed oil in the subarachnoid space.
Intrathecal Injections: A medium sized dog is anesthetized by intraperitoneal injection of 50 mg./kg. of sodium cyclohexylbarbiturate (Evipal). The hair is closely clipped off a wide area over the back of the skull and cervical spine. The dog is then placed on an animal operating table, and the clipped area thoroughly scrubbed with soap, water, and a stiff brush. Next, using sterile technique, the clipped site is cleansed with 70 per cent alcohol, painted with 2 per cent iodine, and again cleansed with 70 per cent alcohol. The prepared area is then draped with sterile towels.

An assistant, gripping the nose of the dog, sharply flexes the head on the chest. This maneuver makes the cisterna magna more accessible by widening the distance between the atlas and the foramen magnum. Observing sterile technique, the operator then determines the location of the occipital protuberance and of the spine of the second cervical vertebra. At a point midway in between these two landmarks, a 20 gauge lumbar puncture needle is pushed through the skin. Again the midpoint between the landmarks is located, and the needle is gently but firmly pushed downward,
always keeping it perpendicular to the skin surface. A fair amount of resistance is met as the dura is pierced, and again when the fibrous tissue over the cistern is reached. At this point the subarachnoid space is a matter of 1-2 mm. from the tip of the needle. Gentle pressure, with great care not to allow the needle to slip, carries the needle into the cistern. Allowing the needle to slip and to pierce too deeply into the cistern may cause irreparable damage to the medulla, often with subarachnoid hemorrhage and death. For this reason it is wise to remove the trochar, attach a 5 cc. sterile syringe, and apply gentle suction to determine if the needle is in the subarachnoid space, whenever the needle passes 1 mm. beyond a resistant layer. Once clear spinal fluid appears in the syringe, 4-7 cc. are withdrawn. One cubic centimeter more of spinal fluid is removed than is to be replaced by the radiopaque compound. This is. 

The compound under study is slowly injected to prevent mechanical elevation of the spinal fluid pressure. /The syringe is then removed, the trochar put back in place. The needle is quickly removed and the dog's head extended to aid in preventing escape of cerebrospinal fluid from the puncture wound.©

The dog is then removed from the operating table, and a lateral radiograph is taken of the head, neck and chest. This is done for

© Direct trauma to the cord by the needle and escape of spinal fluid are to be guarded against. Accidental perforation of a blood vessel in the dura is not infrequent, and the finding of a bloody spinal fluid necessitates discarding the dog from the experimental study.
two reasons: First, as a check to make sure the opaque material was injected into the subarachnoid space; second, to determine the position of the opaque media immediately after injection. Following the injection, the position of the dog determines the level to which the radiopaque material will flow in the subarachnoid space.

As a general rule, the dog's head and thorax are elevated about 20° to insure that the flow of the medium will be away from the ventricles. Usually a small amount of material will reach the ventricular system, but the main mass will flow downward around the lower thoracic and lumbar cord. Occasionally the dog's head is lowered, and the material allowed to flow into the ventricular system.

One to five radiographs are taken on the day of injection to determine the position and mobility of the radiopaque medium. Routinely, radiographs are made every week during the first month, and monthly thereafter until the compound is absorbed or until the dog is sacrificed. After injection, each dog is carefully observed, and its reaction noted until recovery or death. The multiplicity of signs manifested make it hard to judge each dog's reaction exactly. Meningeal irritation seems to be the one symptom common to all, and the degree is evaluated by the stiffness of the neck or spine and evidence of pain on passive flexion of the neck or spine. This method was used by Lindblom (1931). General malaise, anorexia, and definite localizing
Necrological signs (seldom found unless actual trauma to the cord was done during injection), are also taken into consideration in this rough but effective means of analyzing the dog's condition. A few cell counts were done on the spinal fluid to determine more accurately the evidence of inflammatory response, but due to the risk of repeated cisternal puncture and the difficulty encountered in lumbar puncture, this seemed inadvisable. For practical means of reporting the reaction of the large number of animals studied, gradations of meningeal irritation from none to severe are used. The meningeal irritation is of a chemical nature. When actual infection is suspected, cultures of the cerebrospinal fluid are taken.

An autopsy is performed on each animal that is sacrificed or that dies, with special attention to the meninges and central nervous system. The dog is killed by one of two methods: intravenous injection of air or deep ether anesthesia. A cannula is then introduced into the aorta through the left ventricle, and the animal is embalmed with 3 liters of 10 per cent formaldehyde. The central nervous system and meninges are removed intact and are placed in 20 per cent formaldehyde. A radiograph of the brain and cord is made after complete fixation. This is done to find small collections of radiopaque material that may have been obscured by the density of the spinal column.

If any opaque material is present, sections are taken through the area for microscopic study. If no opaque material is evident,
sections are taken through areas where the compound was last visualized by radiography. The microscopic sections are treated with the diamine granule and myelin sheath stain for evidence of nervous tissue damage and with hematoxylin and eosin stain for reaction of the meninges. Cultures of spinal fluid were taken when meningitis was suspected.

Intraperitoneal injections: Both the two compounds that gave evidence of being satisfactory, and with iodized poppy seed oil, the intraperitoneal minimum lethal dose in adult white rats was studied.

Intravenous injections: For the purpose of venography a few intravenous injections were conducted on dogs.

DATA

All of the compounds tested are water white, mobile, light liquids, stable to sterilization.

The data relating to the effect on intrathecal injection of liquid compounds studied are collected in Tables I and II. The compounds in these tables may be divided into two groups. The first group, consisting of a variety of esters of uniodinated and iodinated organic acids, were studied to determine the relation of structure to physiological action. Of this group only ethyl iodobenzoyl-glycolate showed promise. This compound was rather toxic but was absorbed readily. The second

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* Much of this earlier work was done by Dr. J. B. Furst and Dr. C. Dungan with the author in a junior capacity.
Table I

CHEMICAL Meningitis Due to Intrathecral Injections of Various Organic Esters

<table>
<thead>
<tr>
<th>Compound</th>
<th>Dose (cc/ml)</th>
<th>Dogs b</th>
<th>Survival</th>
<th>Death</th>
<th>Chemical Meningitis</th>
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<tr>
<td><strong>Unhalogenated</strong></td>
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<tr>
<td>Ethyl phthalate</td>
<td>0.18-0.22</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>Severe</td>
</tr>
<tr>
<td>Ethyl phenylacetate</td>
<td>0.14-0.25</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>Severe</td>
</tr>
<tr>
<td>Ethyl benzylooctate</td>
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<td>1</td>
<td>0</td>
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<tr>
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<td>Ethyl oleate</td>
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<td>1</td>
<td>0</td>
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<tr>
<td>Tricetin</td>
<td>0.17-0.87</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>Severe</td>
</tr>
<tr>
<td><strong>Halogenated</strong></td>
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<td></td>
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<tr>
<td>Methyl 2-iodostearate</td>
<td>0.60</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>Moderate</td>
</tr>
<tr>
<td>Ethyl 2-iodostearate</td>
<td>0.11-0.28</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>Moderate-severe</td>
</tr>
<tr>
<td>Ethyl iodostearate</td>
<td>0.10-0.23</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>Moderate-severe</td>
</tr>
<tr>
<td>Ethyl iodocholestearate</td>
<td>0.24-0.29</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>Moderate-severe</td>
</tr>
<tr>
<td>Ethyl 1-bromostearate</td>
<td>0.25-0.55</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>Ethyl bromostearate</td>
<td>0.15-0.87</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>Moderate</td>
</tr>
<tr>
<td>Ethyl O-(2-iodobenzyl)-glycolate</td>
<td>0.08-0.15</td>
<td>4</td>
<td>2</td>
<td>3</td>
<td>Severe</td>
</tr>
</tbody>
</table>

**Subarachnoid hemorrhage**
**Trauma to cord**
<table>
<thead>
<tr>
<th>Compound</th>
<th>Dose (mg/kg)</th>
<th>Dose inj.</th>
<th>Survivals</th>
<th>Deaths</th>
<th>Chemical Meningitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethyl O-(2-iodobenzyl)-glycolate</td>
<td>0.08-0.40</td>
<td>7</td>
<td>7</td>
<td>6</td>
<td>Moderate-severe</td>
</tr>
<tr>
<td>Ethyl O-(CH₃)₂-COOCH₂H₅ Type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethyl O-(3-iodophenox)-butyrate</td>
<td>0.25-0.39</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>Moderate</td>
</tr>
<tr>
<td>Ethyl O-(3-iodophenox)-undecylate</td>
<td>0.16-0.28</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>Slight-severe</td>
</tr>
<tr>
<td>Ethyl O-(CH₃)₉-COOCH₂H₅ Type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethyl O-(4-iodophenox)-propionate</td>
<td>0.25-0.32</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>Moderate-severe</td>
</tr>
<tr>
<td>Ethyl O-(4-iodophenox)-butyrate</td>
<td>0.25-0.34</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>Moderate</td>
</tr>
<tr>
<td>Ethyl O-(4-iodophenox)-valerate</td>
<td>0.15-0.30</td>
<td>3</td>
<td>23</td>
<td>3</td>
<td>None-severe</td>
</tr>
<tr>
<td>Ethyl O-(4-iodophenox)-caproate</td>
<td>0.16</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>Severe</td>
</tr>
<tr>
<td>Ethyl O-(4-iodophenox)-heptanoate</td>
<td>0.31</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>Slight</td>
</tr>
<tr>
<td>Ethyl 1-iodophenylundecylate</td>
<td>0.16-0.37</td>
<td>15</td>
<td>14</td>
<td>1*</td>
<td>None-slight</td>
</tr>
<tr>
<td>Ethyl CH₃-COOCH₂H₅ Type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethyl O-(4-iodobenzyl)-butyrate</td>
<td>0.20-0.31</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>Severe</td>
</tr>
<tr>
<td>Ethyl O-(4-iodobenzyl)-caproate</td>
<td>0.25</td>
<td>2</td>
<td>0</td>
<td>3</td>
<td>Severe</td>
</tr>
<tr>
<td>Ethyl C₂(CH₃)₂-COOCH₂H₅ Type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethyl 4-iodobenzyl malonate</td>
<td>0.20-0.34</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>Severe</td>
</tr>
<tr>
<td>Ethyl n-butyl 4-iodobenzyl malonate</td>
<td>0.28</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>Severe</td>
</tr>
</tbody>
</table>

* 1 died with gangrene of small intestine.
group, consisting of thirteen compounds, may be described generally as ethyl esters of iodinated aryl acids. Of this second group, satisfactory results were obtained only with ethyl 4-iodophenyl-valerate, and with ethyl iodophenylundecylate. These two compounds were tested in detail.

Ethyl-\(\omega\)-(4-iodophenyl)-n-valerate: Of the numerous compounds tested, ethyl-\(\omega\)-(4-iodophenyl)-n-valerate was the first to show signs of possibly fulfilling the requirements which had been laid down.

Using the technique outlined, 45 dogs were injected intrathecally with this ester. Thirty-six were injected by cisternal, and 12 by lumbar puncture (Table III).

Following the injection serial radiographs were taken. This compound flowed readily within the subarachnoid space and did not tend to globulate for the first 2 days. Small globules, 1-4 mm. in diameter, of the compound became fixed and within the first 2 weeks encystment was found at autopsy. Ethyl-\(\omega\)-(4-iodophenyl)-n-valerate, by radiograph, disappeared from the subarachnoid space rapidly. No traces could be observed in 8 weeks and often in 6 weeks.

The main difficulty encountered with this radiopaque material was its variable reaction when introduced into the subarachnoid space. During a one-year period, in which 15 dogs were injected, 33 per cent showed no reaction, 22 per cent slight meningeal
<table>
<thead>
<tr>
<th>Deg No.</th>
<th>Kg.</th>
<th>Total dose</th>
<th>dose/gm.</th>
<th>Exitus in days</th>
<th>Chemical meningitis</th>
<th>Reduced activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>37-181</td>
<td>19.0</td>
<td>4.0 cc.</td>
<td>0.22</td>
<td>2</td>
<td>Severe for 2 days</td>
<td>None</td>
</tr>
<tr>
<td>37-206</td>
<td>19.0</td>
<td>4.0 cc.</td>
<td>0.29</td>
<td></td>
<td>None</td>
<td>5</td>
</tr>
<tr>
<td>38-12</td>
<td>15.0</td>
<td>3.0 cc.</td>
<td>0.29</td>
<td></td>
<td>Slight for 1 day</td>
<td>None</td>
</tr>
<tr>
<td>37-206</td>
<td>18.6</td>
<td>4.0 cc.</td>
<td>0.31</td>
<td></td>
<td>None</td>
<td>1</td>
</tr>
<tr>
<td>38-10</td>
<td>16.5</td>
<td>3.0 cc.</td>
<td>0.32</td>
<td>13</td>
<td>Severe for 15 days</td>
<td>None</td>
</tr>
<tr>
<td>38-85</td>
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<td>4.0 cc.</td>
<td>0.29</td>
<td></td>
<td>None</td>
<td>1</td>
</tr>
<tr>
<td>38-63</td>
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<td>0.35</td>
<td>7</td>
<td>Moderate for 7 days</td>
<td>7</td>
</tr>
<tr>
<td>38-57</td>
<td>11.0</td>
<td>3.0 cc.</td>
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<td>10</td>
</tr>
<tr>
<td>37-182</td>
<td>18.2</td>
<td>3.5 cc.</td>
<td>0.30</td>
<td>4</td>
<td>Severe for 4 days</td>
<td>None</td>
</tr>
<tr>
<td>38-107</td>
<td>17.0</td>
<td>3.5 cc.</td>
<td>0.30</td>
<td>6</td>
<td>Moderate for 6 days</td>
<td>None</td>
</tr>
<tr>
<td>38-200</td>
<td>16.0</td>
<td>3.5 cc.</td>
<td>0.31</td>
<td>19</td>
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</tr>
<tr>
<td>38-202</td>
<td>21.0</td>
<td>2.5 cc.</td>
<td>0.24</td>
<td></td>
<td>Slight for 4 days</td>
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</tr>
<tr>
<td>38-167</td>
<td>16.0</td>
<td>3.5 cc.</td>
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<td>24</td>
<td>Moderate for 20 days</td>
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<tr>
<td>38-109</td>
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<td>0.42</td>
<td></td>
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</tr>
<tr>
<td>38-203</td>
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<td>3.6 cc.</td>
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<td></td>
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<tr>
<td>Leg No.</td>
<td>Wgt. kg.</td>
<td>Total dose</td>
<td>Dose gm/kg.</td>
<td>Bruits in days</td>
<td>Chemical meningitis</td>
<td>Days reduced activity</td>
</tr>
<tr>
<td>---------</td>
<td>----------</td>
<td>------------</td>
<td>-------------</td>
<td>----------------</td>
<td>-------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>38-64</td>
<td>20.1</td>
<td>5.5 cc. 0.36</td>
<td>5.05 gm.</td>
<td>-</td>
<td>Slight for 9 days</td>
<td>17</td>
</tr>
<tr>
<td>35-253</td>
<td>20.0</td>
<td>4.0 cc. 0.29</td>
<td>5.75 gm.</td>
<td>3</td>
<td>Severe for 3 days</td>
<td>3</td>
</tr>
<tr>
<td>38-255</td>
<td>12.0</td>
<td>3.5 cc. 0.39</td>
<td>5.03 gm.</td>
<td>-</td>
<td>Slight for 6 days</td>
<td>6</td>
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<tr>
<td>38-301</td>
<td>14.5</td>
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<td>6.45 gm.</td>
<td>-</td>
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<td>0</td>
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<tr>
<td>38-345</td>
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<td>4.5 cc. 0.40</td>
<td>6.45 gm.</td>
<td>-</td>
<td>Slight for 14 days</td>
<td>52</td>
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<tr>
<td>38-332</td>
<td>25.0</td>
<td>4.0 cc. 0.22</td>
<td>5.75 gm.</td>
<td>24</td>
<td>Moderate for 24 days</td>
<td>24</td>
</tr>
<tr>
<td>38-264</td>
<td>22.0</td>
<td>4.0 cc. 0.26</td>
<td>5.75 gm.</td>
<td>12</td>
<td>Moderate for 12 days</td>
<td>12</td>
</tr>
<tr>
<td>38-342</td>
<td>19.0</td>
<td>4.0 cc. 0.30</td>
<td>5.75 gm.</td>
<td>3</td>
<td>Severe for 3 days</td>
<td>3</td>
</tr>
<tr>
<td>38-310</td>
<td>18.0</td>
<td>4.0 cc. 0.32</td>
<td>5.75 gm.</td>
<td>3</td>
<td>Severe for 3 days</td>
<td>3</td>
</tr>
<tr>
<td>38-326</td>
<td>14.0</td>
<td>2.5 cc. 0.56</td>
<td>5.03 gm.</td>
<td>40</td>
<td>Slight for 40 days</td>
<td>40</td>
</tr>
<tr>
<td>37-397</td>
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<td>3.5 cc. 0.24</td>
<td>5.03 gm.</td>
<td>-</td>
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<td>-</td>
</tr>
<tr>
<td>37-2</td>
<td>18.0</td>
<td>4.0 cc. 0.32</td>
<td>5.75 gm.</td>
<td>-</td>
<td>Slight for 2 days</td>
<td>17</td>
</tr>
<tr>
<td>37-160</td>
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<td>4.0 cc. 0.29</td>
<td>5.75 gm.</td>
<td>-</td>
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</tr>
<tr>
<td>38-318</td>
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<td>4.0 cc. 0.32</td>
<td>5.75 gm.</td>
<td>-</td>
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<tr>
<td>38-324</td>
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<td>4.0 cc. 0.29</td>
<td>5.75 gm.</td>
<td>-</td>
<td>Moderate for 7 days</td>
<td>14</td>
</tr>
<tr>
<td>38-348</td>
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<td>4.0 cc. 0.35</td>
<td>5.75 gm.</td>
<td>-</td>
<td>Slight for 6 days</td>
<td>9</td>
</tr>
<tr>
<td>39-19</td>
<td>20.0</td>
<td>4.0 cc. 0.29</td>
<td>5.75 gm.</td>
<td>3</td>
<td>Severe for 3 days</td>
<td>3</td>
</tr>
<tr>
<td>Dog No.</td>
<td>Wgt.</td>
<td>Total dose</td>
<td>Dose/g.</td>
<td>Exitus in days</td>
<td>Chemical meningitis</td>
<td>Days Reduced activity</td>
</tr>
<tr>
<td>---------</td>
<td>-------</td>
<td>------------</td>
<td>---------</td>
<td>----------------</td>
<td>---------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>39-161</td>
<td>16.0</td>
<td>5.5 cc.</td>
<td>0.31</td>
<td></td>
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<td>1</td>
</tr>
<tr>
<td>39-243</td>
<td>12.0</td>
<td>4.0 cc.</td>
<td>0.32</td>
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<td>4</td>
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<tr>
<td>39-201</td>
<td>18.0</td>
<td>6.0 cc.</td>
<td>0.32</td>
<td></td>
<td>None</td>
<td>1</td>
</tr>
<tr>
<td>39-207</td>
<td>20.0</td>
<td>4.0 cc.</td>
<td>0.29</td>
<td>2</td>
<td>Severe for 2 days</td>
<td>2</td>
</tr>
<tr>
<td>39-22</td>
<td>14.0</td>
<td>5.5 cc.</td>
<td>0.36</td>
<td></td>
<td>Moderate on 4th day only</td>
<td>5</td>
</tr>
<tr>
<td>39-201</td>
<td>14.0</td>
<td>5.0 cc.</td>
<td>0.31</td>
<td>1</td>
<td>Severe for 1 day</td>
<td></td>
</tr>
<tr>
<td>39-163</td>
<td>10.0</td>
<td>5.0 cc.</td>
<td>0.43</td>
<td></td>
<td>Moderate for 10 days</td>
<td>11</td>
</tr>
<tr>
<td>39-270</td>
<td>11.0</td>
<td>5.0 cc.</td>
<td>0.39</td>
<td>4</td>
<td>Moderate for 4 days</td>
<td>4</td>
</tr>
<tr>
<td>39-263</td>
<td>11.0</td>
<td>3.0 cc.</td>
<td>0.30</td>
<td></td>
<td>Slight for 4 days</td>
<td>4</td>
</tr>
<tr>
<td>39-222</td>
<td>13.0</td>
<td>3.0 cc.</td>
<td>0.33</td>
<td></td>
<td>Moderate for 9 days</td>
<td>10</td>
</tr>
<tr>
<td>39-287</td>
<td>12.0</td>
<td>3.0 cc.</td>
<td>0.36</td>
<td>2</td>
<td>Moderate for 2 days</td>
<td>2</td>
</tr>
<tr>
<td>39-277</td>
<td>11.0</td>
<td>3.0 cc.</td>
<td>0.39</td>
<td>2</td>
<td>Moderate for 2 days</td>
<td>2</td>
</tr>
<tr>
<td>39-272</td>
<td>10.5</td>
<td>3.0 cc.</td>
<td>0.41</td>
<td></td>
<td>Moderate for 3 days</td>
<td>3</td>
</tr>
<tr>
<td>39-163</td>
<td>11.5</td>
<td>3.0 cc.</td>
<td>0.37</td>
<td></td>
<td>Moderate for 12 days</td>
<td>12</td>
</tr>
<tr>
<td>39-271</td>
<td>13.0</td>
<td>4.0 cc.</td>
<td>0.53</td>
<td>3</td>
<td>Severe for 3 days</td>
<td>3</td>
</tr>
<tr>
<td>39-261</td>
<td>17.0</td>
<td>4.0 cc.</td>
<td>0.34</td>
<td>3</td>
<td>Severe for 3 days</td>
<td>3</td>
</tr>
</tbody>
</table>
irritation, and 45 per cent moderate to severe reactions, 39 per cent of the group dying. At first this high mortality was attributed to impure samples of compound and faulty technique. Therefore, further experiments were performed with pure, sterile samples of radio-opaque media and rigid technique.

After the completion of 48 dog experiments, however, the compound having been injected by both the cisternal and the lumbar route, the results still showed wide variation in reaction of the dogs. Of 48 dogs injected, 25 per cent showed no reaction, 19 per cent slight meningeal reaction, 29 per cent moderate meningeal reaction, and 27 per cent severe reactions. The mortality for the whole group was 45 per cent. The dogs that died survived anywhere from 1-40 days, 65 per cent dying within the first 4 days.

The characteristic, severe reaction of the leptomeninges to ethyl-4-iodophenyl-valerate is shown in dog 38-263, weight 20 kg., which died on the 3rd day after the introduction of 4.0 cc. of the ester into the basilar cistern. Through the post-injection course the dog suffered from a stiff neck, which was very painful on passive motion. His gait was essentially normal.

An autopsy was performed at exitus on the 3rd day, and the brain and cord removed. Grossly nothing abnormal was noted in the central nervous system. Sections taken for microscopic study, however, revealed definite evidence of acute meningitis. The dura and the cord
were not affected.

The subarachnoid space was partly filled with large oval collections of cells surrounding small droplets of the compound introduced. The reaction here is predominantly polymorphonuclear leukocytes and small round cells. Occasionally a few phagocytic cells and a rare eosinophile are seen. The cells were ensnared in a fine fibrin network. The rest of the subarachnoid space was filled with a bluish amorphous appearing substance, through which were scattered nuclear debris and strands of fibrin.

This reaction was seen in all the sections taken from the medullary and cervical regions where the oily compound was seen by radiograph. The subarachnoid spaces in the lower portions of the cord were not abnormal. The reaction was localized around the compound.

In other experiments, in which the dogs suffered from moderate or severe reactions, this same inflammatory response was manifest in various degrees of intensity. As the period of survival increased, the oval collection of cells showed a definite decline in the polymorphonuclear leukocyte response, and an increase in the number of small mononuclears and phagocytic cells. Also, a moderate number of fibroblasts and small capillaries began to appear around the periphery of the droplet.
There is definite increase in the thickness of the arachnoid due to fibroblastic proliferation with dense adhesions of the arachnoid and pia.

Of the 12 dogs in which no symptoms were observed, 4 dogs, sacrificed in 2 and 3 months show a meningeal reaction that is the same as described above, but less extensive. In 4 others no abnormal findings were observed, grossly or microscopically.

**Ethyl iodo phenylundecylate:** Paralleling the experiments on ethyl-\( \omega \)-[4-iodophenyl]-\( \omega \)-valerate, another related compound, ethyl iodo phenyl-undecylate, was studied, which was designed to be more slowly broken down. Employing the same technique, 15 dogs were injected with this compound, 11 by the cisternal and 4 by the lumbar route (Table IV).

As with the previous experiment, serial radiographs were made on each dog. With careful tilting of the animal, the whole cord could be outlined by a thin sheet of compound in 20 minutes. Globulation appeared on the second day. The material, as expected, was not so rapidly absorbed as ethyl-\( \omega \)-[4-iodophenyl]-\( \omega \)-valerate. Some of the animals have been followed for 8 months and there is still some evidence of opaque material within the subarachnoid space. In the radiograph. Absorption of the material occurred rapidly in the first month. From that time on, the disappearance rate was much slower.
<table>
<thead>
<tr>
<th>Dog</th>
<th>Rgt.</th>
<th>Total</th>
<th>Dose</th>
<th>Kritis</th>
<th>Chemical</th>
<th>Days</th>
<th>Reduced activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>28-236</td>
<td>17.0</td>
<td>6.0 cc</td>
<td>0.30</td>
<td>-</td>
<td>Slight en</td>
<td>2</td>
<td>5th day only</td>
</tr>
<tr>
<td>29-233</td>
<td>15.0</td>
<td>6.0 cc</td>
<td>0.34</td>
<td>-</td>
<td>Slight en</td>
<td>2</td>
<td>3rd day only</td>
</tr>
<tr>
<td>29-237</td>
<td>16.0</td>
<td>6.0 cc</td>
<td>0.35</td>
<td>-</td>
<td>Slight en</td>
<td>2</td>
<td>3rd day only</td>
</tr>
<tr>
<td>30-257</td>
<td>12.0</td>
<td>6.0 cc</td>
<td>0.33</td>
<td>-</td>
<td>Moderate en</td>
<td>3</td>
<td>3rd day only</td>
</tr>
<tr>
<td>30-226</td>
<td>12.5</td>
<td>6.0 cc</td>
<td>0.37</td>
<td>-</td>
<td>None</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>39-226</td>
<td>11.0</td>
<td>6.0 cc</td>
<td>0.33</td>
<td>-</td>
<td>None</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>39-306</td>
<td>12.0</td>
<td>6.0 cc</td>
<td>0.34</td>
<td>-</td>
<td>Slight en</td>
<td>2</td>
<td>2nd day only</td>
</tr>
<tr>
<td>39-220</td>
<td>12.0</td>
<td>6.0 cc</td>
<td>0.33</td>
<td>-</td>
<td>None</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>39-313</td>
<td>12.0</td>
<td>6.0 cc</td>
<td>0.33</td>
<td>-</td>
<td>None</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>39-3</td>
<td>12.6</td>
<td>4.0 cc</td>
<td>0.30</td>
<td>-</td>
<td>Slight for</td>
<td>4</td>
<td>4 days</td>
</tr>
<tr>
<td>39-4</td>
<td>16.7</td>
<td>4.0 cc</td>
<td>0.30</td>
<td>-</td>
<td>Severe for</td>
<td>12</td>
<td>4 days</td>
</tr>
<tr>
<td>39-5</td>
<td>11.5</td>
<td>3.0 cc</td>
<td>0.34</td>
<td>-</td>
<td>Slight for</td>
<td>6</td>
<td>6 days</td>
</tr>
<tr>
<td>40-50</td>
<td>14.2</td>
<td>3.0 cc</td>
<td>0.35</td>
<td>-</td>
<td>Slight for</td>
<td>9</td>
<td>9 days</td>
</tr>
<tr>
<td>40-48</td>
<td>11.4</td>
<td>3.0 cc</td>
<td>0.33</td>
<td>24*</td>
<td>Moderate for</td>
<td>6</td>
<td>4 days</td>
</tr>
<tr>
<td>40-51</td>
<td>9.0</td>
<td>2.0 cc</td>
<td>0.43</td>
<td>28*</td>
<td>Moderate for</td>
<td>9</td>
<td>9 days</td>
</tr>
</tbody>
</table>

* Sistempir
* = Peritonitis
The reaction of the dogs to this material was by no means as
variable as that found with ethyl(4-iodophenyl)-m-valerate. Of
the 15 dogs injected with ethyl iodophenyl undecylate, 27 per cent
showed no observable reaction; 46 per cent gave evidence of slight
meningeal reaction lasting 2-9 days with an average of 4-1/2 days;
20 per cent showed a moderate meningeal reaction lasting 3-9 days
with an average of 6 days; 7 per cent showed a severe meningeal
reaction lasting 4 days with a slight meningeal reaction for 6
days and with a total of 12 days of reduced activity. One dog
(40-48) suffered from moderate meningeal reaction for 6 days, fol-
lowed by complete recovery. On the 14th day after injection, 3
days after recovery, the animal developed cherry-red bloody diar-
rhea, failed rapidly and died on the 28th post-operative day.
Autopsy revealed a six inch loop of gangrenous terminal ileum,
apparently due to a volvulus of the intestines.

As previously stated, the dogs tolerated ethyl iodophenyl-
undecylate better than ethyl,4-iodophenyl-m-valerate. The clin-
ical evaluation of meningeal irritation was borne out by the
histological material, with one exception. Dog 39-266, weighing
15 kg., was injected with 4.0 cc. of the ester by the cisternal
route. The post-injection course was complicated by signs of
moderate meningeal irritation on the 3rd and 4th day, followed
by complete recovery. At sacrifice 1-1/2 months later, nothing
abnormal was observed grossly.
However, histological section of the lumbar cord through a small collection of radiopaque medium, revealed definite pathological reaction, in part similar to that observed with ethyl,4-iodophenyl-2-valerate. The dura and cord were not abnormal. The subarachnoid space was filled with large, dense oval collections of cells surrounding small droplets of oil. In contrast to the polymorphonuclear leukocyte response with ethyl,4-iodophenyl-2-valerate, a predominant mononuclear response was observed with this compound. There were moderate numbers of phagocytes and fibroblasts, a few polymorphonuclear leukocytes and plasma cells. The cells were supported by a fine network of fibrous tissue. This network of fibrous tissue had produced adhesions between nerve roots, the arachnoid, and the pia.

Two other sections from the same cord showed a few small oval collections of cells, as described above, but the majority of the subarachnoid space was free of any reaction.

The more common finding was that seen in dog 39-290, weight 20 kg. Five cubic centimeters of the ester were injected cisternally. The day following injection the dog was sluggish, with no evidence of meningeal irritation. On the second day he was apparently normal and remained so until sacrificed 1-1/2 months later. Sections taken through the cord where the compound was last demonstrated by radiograph, showed a few cystic areas up to 1 mm. in diameter in the subarachnoid space. The walls of these cysts were
made of a thin layer of fibrous tissue in which a few small mononuclears and phagocytes were seen. A few polymorphonuclear leukocytes were also observed. The rest of the space was free of reaction and sections taken where the opaque material had been observed previously by radiograph now showed no reaction.

One dog, 39-253, recovered completely 2 days after the intrathecal injection of 3.0 cc. of this ester. Six months after injection he developed a generalized weakness of his legs and an inability to walk any distance without support. At present he has improved to some extent. He is being carefully watched and will be sacrificed when he begins to fail. This is a reaction not observed before with any compound tested, and it is deemed advisable to postpone sacrificing the dog until whatever process is causing the generalized weakness has had an opportunity to cause definite pathological changes in the cord.

Iodized Poppy Seed Oil: For the purpose of comparison with the new compounds under study, iodized poppy seed oil (lipiodol), a very viscous light yellow oily compound, was injected cisternally into 9 dogs (Table V). This material was chosen as it is the most widely used and accepted today. The actual injection of this compound is difficult and considerable pressure must be exerted on the syringe plunger to force the iodized oil into the subarachnoid space, even when the oil and syringe have been warmed to body temperature.
Table V
Iodinated Pappy Seed Oil - Intrathecal Injection

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>Ugt. kg.</th>
<th>Total dose</th>
<th>Dose ga./kg.</th>
<th>Iritis in days</th>
<th>Chemical meningitis</th>
<th>Days Reduced activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>38-168</td>
<td>13.0</td>
<td>2.75 cc.</td>
<td>0.26</td>
<td>-</td>
<td>Moderate</td>
<td>5 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.70 gm.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>38-201</td>
<td>24.0</td>
<td>3.5 cc.</td>
<td>0.20</td>
<td>-</td>
<td>Slight</td>
<td>6 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.70 gm.</td>
<td></td>
<td></td>
<td>for 2 days</td>
<td></td>
</tr>
<tr>
<td>38-319</td>
<td>16.0</td>
<td>3.5 cc.</td>
<td>0.29</td>
<td>-</td>
<td>Slight</td>
<td>5 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.70 gm.</td>
<td></td>
<td></td>
<td>for 4 days</td>
<td></td>
</tr>
<tr>
<td>38-332</td>
<td>26.0</td>
<td>4.0 cc.</td>
<td>0.20</td>
<td>24</td>
<td>Moderate for 24</td>
<td>24 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5.35 gm.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40-12</td>
<td>24.0</td>
<td>4.5 cc.</td>
<td>0.25</td>
<td>-</td>
<td>Moderate for 28</td>
<td>28 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6.0 gm.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>37-27</td>
<td>16.9</td>
<td>3.0 cc.</td>
<td>0.24</td>
<td>-</td>
<td>Moderate for 14</td>
<td>14 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.0 gm.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>38-8</td>
<td>17.0</td>
<td>4.0 cc.</td>
<td>0.31</td>
<td>-</td>
<td>Slight for 16</td>
<td>16 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5.35 gm.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>39-1</td>
<td>9.0</td>
<td>3.0 cc.</td>
<td>0.44</td>
<td>-</td>
<td>Moderate for 14</td>
<td>14 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.0 gm.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40-11</td>
<td>10.0</td>
<td>3.0 cc.</td>
<td>0.40</td>
<td>-</td>
<td>Moderate for 14</td>
<td>14 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.0 gm.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Following the injection of the radio opaque medium, radiographs were made at definite intervals on each animal. Tilting of the dog after injection produced very slow movement of the compound in the subarachnoid space. This is a common clinical finding. Often one hour at 45° elevation would not cause the material to flow down into the lumbar sac. The degree of elevation had to be carefully watched or the material would break up and two or more separate opaque masses would be visualized. Globulation usually occurred within the first week. Up to two months, much of the iodized oil would remain free to move; however, small opaque masses 2-4 mm. in diameter could readily be visualized that did not move on change of position. At eight months approximately, three-quarters of the material in the spinal canal was fixed so no amount of tilting would affect the movement of the material.

Radiographs made over a period of 8 months, showed only minimal evidence of disappearance of this iodized oil.

As was expected from published clinical and experimental evidence, the mortality with iodized poppy seed oil was low. Of the 9 dogs injected, only 1 died (24 days after injection). This dog showed evidence of moderate meningeal irritation throughout his post-injection course. At autopsy a subarachnoid hemorrhage was found near the site of injection and is probably responsible for the exitus, in part at least. This one dog with subarachnoid hemorrhage is included because
the clinical appearance and symptoms did not make it possible to
say that the hemorrhage and not the compound was responsible for
the dog's death. Eighty percent of the dogs recovered, 33 percent
suffering from slight meningeal irritation lasting from 2 to 16
days, an average of 7 days. Sixty-seven percent gave evidence of
moderate meningeal irritation, lasting 5 to 28 days, with an average
of 16-1/2 days. Meningeal irritation slight or moderate was observed
in every dog.

With iodinated poppy seed oil, the pathological findings are
in some respects similar to those found with undecylate, but appear
to cause greater mechanical damage.

Dog No. 12, weighing 25 kg., was injected with 4.5 cc. of the oil
cisternally. Throughout the post-injection course there were signs
of moderate meningeal irritation. The dog was sacrificed one month
after injection. At autopsy nothing abnormal was found grossly.
Sections were taken through areas of the cord that showed the presence
of opaque material by radiograph. Free oil flowed from the cut section
of the cord. The dura and spinal cord were not abnormal. In the
subarachnoid space, two cysts of 1-2 mm. in size, locally occupying
the whole subarachnoid space, and numerous smaller cysts were seen.
The walls of these cysts were made up of fibrous tissue of varying
thickness, in which the predominant cells were small mononuclears
and phagocytes and a moderate number of polymorphonuclear leukocytes.
The development of the fibrous cyst walls has been accompanied by adhesions between the arachnoid pia and nerve roots. With minor variations in the size and number of cysts this is the typical picture seen with iodinated poppy seed oil.

A complication seen in 2 dogs is shown well by dog 40-11. This dog, weighing 11.6 kg. was injected with 2.9 cc. of the iodinated oil cisternally. During the post-injection course the dog showed no observable abnormal reactions. Radiographs revealed the presence of opaque material throughout the cord, and small amounts in the ventricles. He was sacrificed 6 weeks after injection. At autopsy the central canal and ventricles were dilated three to four times normal size. Two small globules, 2 mm. in diameter, were found free in the third ventricle. Sections taken through the cord revealed multiple cystic areas already described, and marked dilatation of the central canal without evidence of any acute or chronic reaction in the tissues about the canal, but definite compression and loss in amount of the cord tissue. It is suspected that the oil within the ventricular system blocked the foramina of Luschka and Magendie, and partially prevented the escape of cerebrospinal fluid into the subarachnoid space and caused a hydrocephalus.

**Intraperitoneal injections (Table VI):** Ethyl 

\[ \text{Ethyl}_{10} \text{Iodophenyl-} \text{valerate, when injected intraperitoneally in white rats, showed a minimum lethal dose of 2.5 cc. per kilogram of body weight. Through the} \]
# Table VI

Toxicity Intraperitoneally in White Rats

<table>
<thead>
<tr>
<th>Compound</th>
<th>M.L.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethyl $\beta$-iodophenyl-valerate</td>
<td>2.5 cc./kg.</td>
</tr>
<tr>
<td>Ethyl $\alpha$-iodophenylundecylate</td>
<td>16.0 cc./kg.</td>
</tr>
<tr>
<td>Iodinated poppy seed oil</td>
<td>above 25.0 cc./kg.</td>
</tr>
</tbody>
</table>

# Table VII

Degree of Chemical Meningitis and Mortality

<table>
<thead>
<tr>
<th>Dogs inj.</th>
<th>None</th>
<th>Slight</th>
<th>Moderate</th>
<th>Severe</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethyl $\beta$-iodophenyl-$\alpha$-valerate</td>
<td>48</td>
<td>25%</td>
<td>19%</td>
<td>25%</td>
<td>27%</td>
</tr>
<tr>
<td>Ethyl $\alpha$-iodophenyl undecylate</td>
<td>15</td>
<td>27%</td>
<td>46%</td>
<td>20%</td>
<td>7%</td>
</tr>
<tr>
<td>Iodinated Poppy Seed Oil</td>
<td>9</td>
<td>0</td>
<td>33%</td>
<td>67%</td>
<td>0</td>
</tr>
</tbody>
</table>
Use of radiograph, it was determined that the material disappears within 2 weeks in the surviving rats. At autopsy no trace of the compound could be detected after 2 weeks. The peritoneal surfaces showed no gross signs of irritation after 2 weeks. Only in those rats dying with the lethal dose could slight hyperemia and a small amount of diffuse dull reddening of the peritoneal surfaces be observed.

The minimum lethal dose of ethyl iodophenylundecylate when injected intraperitoneally in white rats was 16.0 cc. per kilogram of body weight. The compound disappeared by radiograph within 6 weeks. The rats that survived, at autopsy showed no evidence of the opaque material and no gross peritoneal reaction. In those rats dying of a lethal dose, small amounts of cheesy, white material were found lying between the folds of intestines. In this case only small areas directly in contact with the compound showed any reaction. Here there was slight reddening and hyperemia of the serous membrane. There was no generalized reaction.

Using iodinated poppy seed oil, no definite minimum lethal dose by peritoneal injection was obtained. Amounts as high as 25 cc. per kilogram were introduced and well tolerated by the white rats. This confirms the findings of Crandall and Walsh (1931). By radiograph and at autopsy, even after 2 months, and in 2 rats at 7 months, the iodized oil was still present. It was a dark brown
cheesy mass lying between the loops of intestine. There was a localized edema and hyperemia of the serous surfaces in direct contact with the iodized oil.

**Intravenous injections:** Ethyl (4-iodophenyl) valerate. One dog weighing 7.2 kg. was injected intravenously with 0.42 cc. per kilo. There was no immediate reaction. On one-half hour the dog vomited and remained groggy for two hours. In 12 hours the dog had fully recovered and showed no sequelae.

Ethyl iodophenyl undecylate. Four dogs were injected intravenously with this compound in doses varying from 0.23 cc. per kg. to 1.0 cc. per kg. Two dogs receiving 0.23 and 0.25 cc. per kg. suffered no immediate or delayed effects. The dog receiving 0.45 cc. per kg. became nauseated in 10 minutes and remained ataxic for 2 hours, followed by complete recovery. The dog receiving 1.0 cc. per kg. became nauseated and vomited in 35 minutes, developed ataxia in 45 minutes, and became comatose in one hour. The dog died 6 hours after injection. Sections of lung, liver and spleen showed no evidence of the oily compound in the capillaries. The brain was not examined.
SUMMARY

Of the 26 compounds injected intrathecally in dogs, the ethyl esters of iodinated aryl acids gave evidence of satisfying to some extent the requirements outlined for our purposes. Of the 13 compounds studied in this group, ethyl-4-iodophenyl-valerate and ethyl iodophenylundecylate appeared to be the most suitable although not entirely satisfactory for subarachnoid injection in dogs (Table VII). After the completion of 48 intrathecal injections in dogs, the mortality with ethyl-4-iodophenyl-valerate remained high, 45 per cent. Therefore this compound was rejected for intrathecal use, but has been found suitable for other body cavities, nasal sinuses and fistula tracts (unpublished data, to be reported).

The fifteen dogs injected intrathecally with ethyl iodophenyl-undecylate appeared to tolerate this compound well. The mortality was low - 7 per cent. The degree of chemical meningitis was never severe or persisted for more than 12 days. The pathological studies reveal definite reaction to the material wherever it is present, but not as severe as with iodized poppy seed oil. This compound gradually disappears over the period of 5 to 12 months.

Iodized poppy seed oil, studied for the purpose of comparison, is also well tolerated intrathecally in dogs. The degree of chemical meningitis is never severe, but may persist for 3 to 4 weeks. The mortality is 11 per cent. The compound disappears slowly, and is
apparently a matter of years. Pathological studies reveal definite reaction around the oil present in the subarachnoid space. In 2 dogs an internal hydrocephalus developed following the use of the oil.

The advantages of ethyl iodophenylmaleate over iodinated poppy seed oil are the following:

1. It is more fluid

2. The initial period of meningeal irritation is shorter

3. It disappears rapidly at first, then slowly, from the subarachnoid space.

4. The pathological reaction, although definite, is not widespread, and does not persist after the compound has been absorbed.

The disadvantages of this compound are the following:

1. At times it causes meningeal irritation, clinically

2. Definite pathological changes are observed after its use in the subarachnoid space

3. It tends to coagulate in 2 days. This may be corrected by modifying the technique of examining the dog.
CONCLUSIONS

1. Of the 26 ethyl esters of various iodinated organic acids, only ethyl iodophenylundecynoate seems suitable for myelography.

2. Ethyl iodophenyl undecynoate appears to be absorbed and as long as any of the ester is present there is some pathological reaction about the compound.

3. Comparative tests with the standard iodized poppy seed oil show a definite but different pathological response which persists indefinitely, since the compound is very slowly absorbed.

4. Ethyl - w- (4-iodophenyl)-o-valerate, although not suitable for myelography, has found clinical application as a contrast medium.
BIBLIOGRAPHY


Locherini, T. (1936), Sull' utilia diagnosi delle esplosioni radiolipiodolica endocraneale in speciali casi di nevralgie chiatica e sul moto pratico per terliore del senso spinale il lipiodol introdotto. Felici (con.pract.) 43, 378.


Rendall, S. N. (1935), Comparison of the use of transuterine insufflation with carbon dioxide and roentgenolymphography taken after the injection of iodine oil. Radiology, 32, 579.


EASTMAN KODAK COMPANY
ROCHESTER 1, N.Y.

January 8, 1943

Lafayette Pharmaceutical Inc.
Lafayette, Indiana

Attention of Mr. W. S. Bucke

Gentlemen:

With respect to your request for permission to use our trade-mark PANFROGLUX upon packages and/or vials containing contrast media for radiography and prepared from bulk quantities thereof, we shall be pleased to extend to you such permission on a non-exclusive basis in return for your undertaking to fulfill or comply with the conditions necessary under such circumstances to protect our ownership and rights in and to said trade-mark PANFROGLUX and the good-will therein.

The primary function of a trade-mark is to indicate the origin of goods and the proper maintenance of a trade-mark, particularly when licensed for use by others, requires that the mark be used only on goods having a common origin or under the same control as other goods bearing the same trade-mark. Our grant to you of a non-exclusive license to use our trade-mark PANFROGLUX is therefore made subject to certain conditions, namely:

1. That you at all times acknowledge our ownership of and rights in and to the trade-mark PANFROGLUX as applied to radiographic contrast media and similar goods, that said trade-mark PANFROGLUX will be used by you only on radiographic contrast media sold by you under said trade-mark PANFROGLUX, that the packages and/or vials of such contrast media shall conform to standards of quality and stability prescribed or approved by us and shall be legibly marked "Trade-Mark PANFROGLUX - Licensed by Proprietor" and "Packaged by Lafayette Pharmaceutical Inc." that we shall have the right of approval of your packages, labels, advertising, promotional matter, etc. insofar as reference to the trade-mark PANFROGLUX is concerned; and that such non-exclusive
Lafayette Pharmaceutical Inc. -- 2

January 8, 1943

License is automatically terminated without further notice
upon any use by you of said trade-mark PANORAMIC in a
manner inconsistent with the foregoing conditions or our
ownership of and rights in and to said trade-mark PANORAMIC.

Acceptance of this license and agreement to abide
by the aforesaid conditions will be established by return of
the attached duplicate of this letter signed by an officer
of your company.

Yours very truly,

EASTMAN KODAK COMPANY

[Signature]
Secretary

The conditions of the foregoing letter are accepted.

January 18, 1943

LAFAYETTE PHARMACEUTICAL INC.

[Signature]

[Title of Officer]
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3. Comparative tests with the standard iodized poppy seed oil show a definite but different pathological response which persists indefinitely, since the compound is very slowly absorbed.

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