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On the Effects of Various Iodized Oils on the Meninges.[1]

By

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In a paper published in 1928,[2] Odin and Runström reported on a method devised by them of obtaining an iodized oil especially adapted to the purpose of myelography. In distinction to the iodized oils on the market, this oil irritates the meninges only very slightly or not at all. The former oils, when injected in the amount necessary for exact X-ray diagnosis (5 to 10 cm^3), give rise to such severe chemical meningitis, that they are not suitable for use in myelography. The experimental work of the mentioned research was carried out by the author of this paper, who in the course of it became interested in the problem of ascertaining which of the components of the oils in question were the cause of the chemical meningitis.

It has proved rather difficult to solve this problem; the experimental work has been extensive and has taken much time. The chemical work has also been fraught with difficulties. The required oils were produced by prof. Thor Ekekrantz, Ph. D., who has an extraordinarily wide and varied experience acquired in the course of many years' research in the field of organic medicine; he has assisted me with important advice and information, for which I hereby extend to him my sincerest thanks.

At the very beginning of my investigations, I perceived the necessity of making *large series of experiments*. The expenses of the investigation were, to be sure, increased thereby, but my results

[1] Submitted for publication in swedish manuscript April 18, 1931.
[2] Iodized oils as an aid to the diagnosis of lesions of the spinal cord, Acta radiol., suppl. VII, 1928.

were also more reliable. In my experiments, I used rabbits, and found that these animals' reactions, even with the most precise methods of injection, are subject to rather large individual variations. To what this may be due is hard to say, but an important factor appears to me to be the circumstance that the rabbits offered for sale are usually mixed breeds, with the dominant qualities of the different breeds producing varying degrees of susceptibility to definite irritants. The following experiment confirms this assumption: Four rabbits were given subarachnoid injections with $^1/_2$ cm^3 iodized poppy oil (acidity, 2.5). The rabbits were about the same size. Two of them were black, one was yellow and one white. The two black rabbits died in the first twenty-four hours with violent symptoms of meningitis. The general condition of the two remaining animals was only moderately affected for the first forty-eight hours. After three days, there were no symptoms, and the animals were killed. The histological examination nevertheless revealed cell infiltration in the meninges, most pronounced in the first two animals, and less so in the last two. Bacterial staining gave negative results in all four cases.

Another factor which may be very significant in certain cases is the presence or absence of catalytic agents. This is quite plain from two series of experiments with the relatively unstable substances ethyl iodide and ethylene iodide. These substances, which can be perfectly neutralized and freed of all impurities, produce only slight meningitis or none at all in some cases, and extremely severe meningitis terminating in death in others.

As it became evident after a period of experimentation that the iodized vegetable oils and the iodized animal oils have a fundamentally different effect on the meninges, these two kinds of oil will be treated separately.

Effect of the iodized vegetable oils on the meninges.

The degree of irritation of the meninges was found to vary considerably with the use of different oils. Certain oils, such as sesame oil, produced very slight irritation or none at all, while others, such as poppy oil, produced severe meningitis. The irritation was found to be proportionate with the content of free fatty acid[1] in the oil, i. e., the acidity as indicated in the following table:

[1] By fatty acids, the author means aliphatic monocarbonic acids under the general formulas $C_nH_{2n-1} \cdot COOH$ and $C_nH_{2n-3} \cdot COOH$.

Oil	Acidity	Degree of irritation
Soy	0.3	None
Sesame	0.6	»
Almond	1.2	Pronounced
Linseed	2.2	»
Poppy, refined	2.4	Moderate
» ordinary	6.5	Extreme

This was even plainer in experiments in which the same iodized oil was used, though the acidity differed. The following series of experiments in which iodized sesame oil was used is a clear proof:

Acidity	Degree of irritation
0.6	None
3.69	Moderate (rabbits died within 3 days)
6.5	Extreme (rabbits died within half an hour)

It was further found that the iodized product of an oil caused greater irritation than the oil itself, which proved to be due to the fact that the free fatty acid was transformed during iodization into iodic fatty acid, which has a considerably higher acidity than the free fatty acid.

The oil that is to be used for iodization should therefore contain the least possible amount of free fatty acid. However, it was found that it was not sufficient to select an oil that *usually* has a low acid content, e. g., sesame oil, but that it was necessary to control the acid content of the oil before use in each individual case. The content of free fatty acid is not constant; if the oil is unsuitably stored, it is split, and fatty acid is set free (rancidity).

During and after iodization, another impurity may develop which is at least equally important with that of free fatty acid and iodic fatty acid, viz., hydrogen iodide.

Hydrogen iodide is formed by hydrolysis during or after the preparation of the oil. The cause of its formation appears to be either that the iodine substitution product has not been adequately dried, or that the oil was not adequately protected from the absorption of moisture during storage. As the degree of hydrolyzation is apparently dependent on the temperature, the decomposition of the oil is hastened by too high a temperature. It has also been found that an iodized oil to which the maximum amount of iodine has been added is more susceptible to hydrolysis than a not fully iodized one. When hydrolysis has once started, it continues ever more rapidly, with the developing hydrogen iodide functioning as a sort of catalytic agent. Iodine is precipitated out from the hydrogen iodide, giving the iodized oil a darker shade.

The irritation arising from the use of vegetable oils is thus due to impurities in the shape of free fatty acids or iodic fatty acid, as well as under certain conditions, hydrogen iodide.

These *impurities are resorbed comparatively easily,* while the iodized oil itself is slowly resorbed. This circumstance is the probable cause of the excentric course of the iodine elimination curve. For if an impure iodized oil, e. g., lipiodol Lafay, is injected, a high elimination of iodine will be found shortly after the injection; the elimination curve falls quite rapidly, and after all impurities have been resorbed, it runs along an almost straight line (figs 1 and 2). The curves differ somewhat in subarachnoid and in intra-

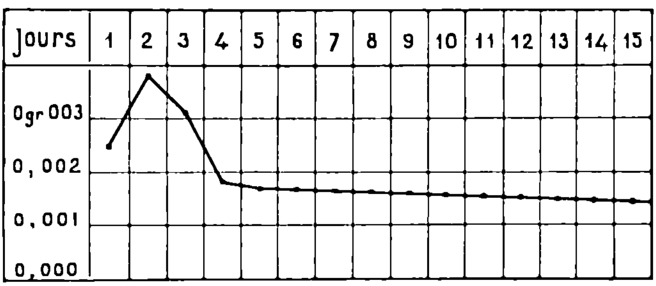

Fig. 1. Renal elimination of iodine after subarachnoid injection of lipiodol Lafay (Sicard and Forestier).

tracheal injection. In the former, the initial fall of the curve is very much more gradual than in the latter. The author believes this is due to the circumstance that the iodized oil in *subarachnoid injection* is distributed in fairly large lakes, whereby the contact between the organ and the iodized oil is limited to a rather small surface, which prevents rapid resorption of the iodine-holding impurities (fig. 1). In *intratracheal injection,* on the other hand, the iodized oil is aspirated rapidly into the terminal bronchi and alveoli, being thereby finely distributed, so that the contact surface between the organ and the iodized oil is comparatively large. The resorption ot the impurities is therefore undoubtedly hastened; the elimination of iodine will be greatest the first day, and will thereafter diminish very rapidly (fig. 2).

When the aforementioned impurities have been resorbed, the resorption of the iodized oil proceeds very slowly. The time required for resorption differs somewhat in the different groups; the resorption takes place particularly slowly in the subarachnoid cavity, in which the oil may be retained for years. Some time after the injection of oils that are resorbed with difficulty, a sort of pseudotumour may be found in certain organs, so-called *fatty granulomata*. These may for instance be found in the subcutaneous connective tissue after the injection of large quantities of camphor oil.[1] It is therefore reasonable to suppose that such formations may also appear in the subarachnoid cavity. The author was in

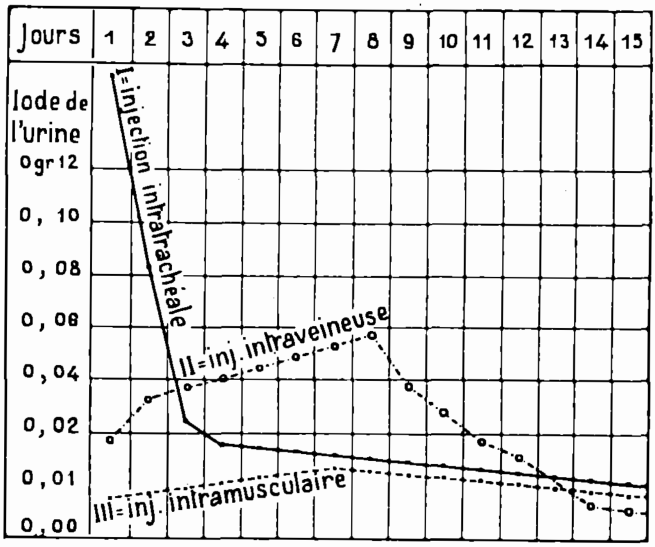

Fig. 2. Renal elimination of iodine after intratracheal injection of lipiodol Lafay (Sicard and Forestier).

previous experiments unable to demonstrate the presence of any fatty lipomata four months after the injection of lipiodol Lafay (iodized poppy oil).[2] As this interval of time may have been too short, further experiments were made with iodized sesame oil. Two rabbits were given injections of 1 cm³ each. They were killed after half a year. Before the brains were extracted, the skulls were X-rayed. In the one, the oil was found to have collected in large lakes, while in the other, it was distributed in numerous small droplets. When the brain was removed in the former case, it was found to contain two large lakes of oil, surrounded and interfoliated with new-grown connective tissue. At a third place, there

[1] Henschen, K. — Ueber subcutane Fremdkörpergeschwülste aus nicht resorb. Kampferölinjektionen, Verh. d. deutsch. pathol Gesellsch., xvii, 1914, 342—346.
[2] On the effect of lipiodol on the meninges, Acta radiol., vol. 5, 1926, 129—134.

was a pachymeningitic surface which was on incision also found to contain droplets of oil (fig. 3). The histologic examination showed that these formations consisted of fatty phagocytes of various sizes; they were surrounded or permeated with new-grown connective tissue, some of it indurated (fig. 4). In other words, they presented the *typical picture of fatty granuloma*. In the other specimen, in which the oil was separated into small droplets, there were no granulomata; we found only numerous small oil droplets in the arachnoid membrane, but no reaction.

The literature mentions a few cases of dissection on humans after lipiodol injection into the subarachnoid cavity; judging from the histologic examinations, it seems likely that fatty granulomata were present in some of these.[1] *It is thus probable that the injection of vegetable oils into the subarachnoid cavity may under certain circumstances give rise to fatty granulomata.* Judging from the mentioned experiments, it seems most probable that granulomata develop when the oil gathers in large lakes. To determine this question, more extensive investigations are naturally required; further investigation should also determine whether or not these granulomata have any clinical significance. *However, the circumstance that there is a risk of such a development of granulomata demands that myelography with iodized oils should be made only in those cases in which there is a genuine indication for such an examination.*

Effect of animal oils on the meninges.

As mentioned before, the effect of animal oils is quite a different one from that of the vegetable oils, this difference apparently being due mainly to differences in resorption. The only animal oils which could be regarded as suitable for experiment were cod liver oil (acidity 1.3) and lard oil (acidity 1.2). The author has tested only the former, as the latter is very hard to obtain in a smooth and perfect condition.

Only 24 hours after its injection, the iodized cod liver oil was found to be already thoroughly emulsified; the subarachnoid cavity was filled with a milky liquid which was found under the

[1] Sicard et Forestier — Diagnostic et thérapeutique par lipiodol, Paris 1928. Pinéas — Eigenartiger Hirnbefund nach Encephalographi mit Iodipin ascendens, Zentralbl. f. d. ges. Neurologie, 1927, 910—911.
Simons, et alii.

microscope to consist in small droplets of oil. The oil was plainly in the process of rapid resorption, and series of experiments also proved that this oil is resorbed quite rapidly. The experimental animals as a rule already showed signs of meningitis a few hours after injection. The meningitis speedily exacerbated, and most of the animals died one or two days after injection. But even in these experiments, individual variations were manifest. In a few cases, the animals survived the severest period of meningitis, which improved as the oil was resorbed (controlled by X-ray examination).

In these cases, the meningitis was not caused by any impurities like those mentioned before, as the acidity could by certain purefying processes be reduced to 0.65, i. e., about the same as that of sesame oil, and no hydrogen iodide was present. The meningitis must have been caused by products of decomposition when the oil was split. Through emulsification, the cerebrospinal fluid presents an enormous surface to the action of the oil, and the products of splitting (oxyacids and glycerine) are dissolved in the cerebrospinal fluid and irritate the meninges.

In intratracheal injection, iodized cod liver oil also produces powerful irritation. After such injections, the experimental animals died in one half to one and a half days, and dissection revealed numerous areas of bronchopneumonia (purulent or fibrous) wherever the oil was present. These cases were also examined for the possible presence of bacterial infection, but none was found.

The comparatively rapid resorption of the iodized animal oils obviates the risk of any formation of fatty granulomata. In this respect, they are therefore probably to be preferred to the vegetable oils; however, the circumstance that the products of splitting call forth strong irritation, particularly of the meninges, probably makes it impossible to use them as a contrast medium in X-ray examination.

Summary.

The author reports on a continuation of his experimental investigation of the biological effects of iodized oils. He has studied the effect of both animal and vegetable iodized oils on the meninges. In the *vegetable oils*, the irritation is produced by impurities, mainly *fatty acids* or *iodic fatty acid*, sometimes also *hydrogen iodide*. When there are no such impurities, no irritation arises in the ex-

perimental animals. These impurities are resorbed rather quickly, while the iodized oil itself is resorbed very slowly. Under certain circumstances, such an oil may give rise to socalled *fatty granulomata*. *Iodized animal oils*, such as cod liver oil, produce severe meningitis, even when there are no impurities. This is due to the fact that the oil is emulsified by the cerebrospinal fluid, after which rapid splitting takes place. The products of splitting thus formed have a powerfully irritating effect on the meninges. For this reaon, it seems that they can not be used as contrast media.

Fig. 3. Rabbit brain with fatty granulomata appearing at the back of the cerebrum and cerebellum (rich yellow colour). To the left in the cerebrum, a pachymeningitic area remaining after a fatty granuloma.

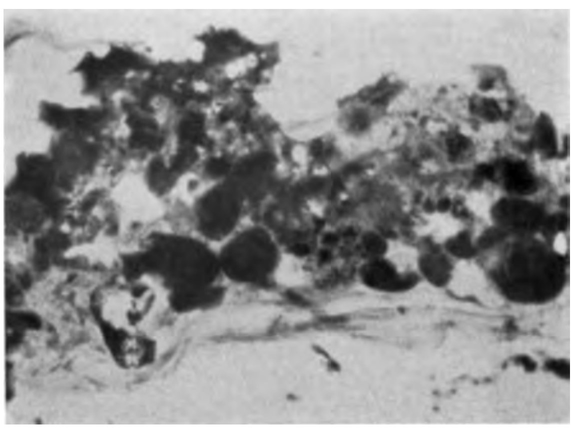

Fig. 4. Microscopic view of fatty granuloma. The oil, stained black with osmium, appears in droplets of different sizes, imbedded in new-grown connective tissue, some of it indurated.