Introduction

Millions of people living in iodine-deficient areas and suffering from goiter, growth and mental retardation, or cretinism have benefited from iodine supplementation with iodized oils. Except for long-standing fibrous multinodular glands, goiters diminish in size or disappear; hypothyroidism is reversed, mental retardation is arrested, and the incidence of new cretinism is reduced. More importantly, prophylactic use of iodized oil (mostly Lipiodol) prevents nearly all of these complications (4, 7, 9, 13, 16, 19, 20, 25, 30, 32, 33, 43, 46, 53, 60, 67, 70, 73, 86, 88, 89, 112, 113, 115, 120). Nevertheless, many more millions remain untreated; it is estimated that currently only about half the population in 83 developing countries receive an adequate iodine supply (44). Hence it is pertinent to look at the physiologic and pharmacologic aspects of iodized oil administration to understand better the mechanism of action and the risks involved in its future use.

In addition to its widespread use in the treatment and prophylaxis of endemic goiter, there is a vast literature describing the use of Lipiodol (also called Ethiodol) in larger dosage: 1) As contrast medium for hysterosalpingography, lymphography, amniography, and myelography in the past; and 2) For detection and treatment of hepatocellular carcinoma by intraarterial (hepatic artery) injection. Lipiodol is preferentially accumulated in vascular hepatomas relative to adjacent liver tissue, approaching a concentration ratio of $10^3$. There is also a 20%–30% longer effective half-life in the tumor versus normal liver. To what extent this is due to local embolization is not clear. This localization can be used for 4 different purposes: a) detection of small lesions; b) embolization of the tumor, alone or with gelfoam or other particulate matter; c) localized delivery of chemotherapeutic agents such as cisplatin, adriamycin, neocarzinostatin, etc; and d) reasonably localized internal radiation by use of $^{131}$I-Lipiodol. The latter can be readily produced by iodination of unsaturated oils with labeled iodine or by 1 of several exchange methods using previously iodized oil and an oxidized form of the radioisotope; this yields material of high radiochemical purity. Certain lessons learned from these uses are instructive for studies relating to goiter prophylaxis.

Chemistry

Lipiodol and related compounds are products of the addition (not substitution) of iodine to double bonds of the unsaturated fatty acids of certain plant oils, most of which have a very high percentage of unsaturated fatty acids. Historically this procedure stems from the determination of the "iodine number" used to estimate the number of double bonds in such oils (grams of iodine incorporated per 100 grams of oil). Recently more reactive iodinating agents such as IBr, ICl or HI (38, 52) have been used to speed the reaction, but adding only 1 iodine atom per double bond:

$$\text{CH}_3(\text{CH}_2)_m\text{CH} = \text{CH(\text{CH}_2)_n\text{COOH} + HI} \rightarrow \text{CH}_3(\text{CH}_2)_m\text{CHICH}_2(\text{CH}_2)_n\text{COOH}$$

When the double bond is near the center of a long-chain fatty acid, as in the case of oleic acid, the location of the iodine atom is random between the 2 unsaturated carbons. Assuming the reaction goes to completion, the degree of iodination will depend on the number of double bonds present in the substrate oil. The predominant products are, therefore, mono-, di-, and tri-iodostearic acids, being derived from oleic (C18:1), linoleic(C18:2), and linolenic(C18:3) acids present as triglycerides in the plant oil. Shorter and longer chain unsaturated fatty acids will, of course, also be iodinated, but their abundance in the oils usually employed is low.

Iodinated triglycerides tend to be too viscous for easy parenteral use but are satisfactory for oral use. By contrast, the singly esterified fatty acids (as ethyl esters) derived from the iodinated triglycerides, for example, Lipiodol or Ethiodol, are much less viscous. These are derived from poppy seed oil whose
fatty acids are 98% unsaturated. Oriodol is the more viscous, iodinated triglyceride from poppy seed oil for oral use. The composition of various iodinated oils is listed in Table 1. It should be emphasized that there are many oils with abundant mono-, di-, and tri-unsaturated fatty acids that iodinate well and yield a useful iodine content. Their use in countries where such oils are available and cheap should be encouraged, especially for oral use.

Lipiodol/Ethiodol is stabilized with 1% poppy seed oil, contains 37%-38% iodine, and with a specific gravity of + 1.25–1.28 g/mL contains ~475 mg iodine per mL; it has a viscosity of 0.5–1.0 poise and is soluble in various organic solvents but not water. It is available under the names Lipiodol UF (ultrafluide) or Ethiodol, and is supplied by Guerbet Laboratoires, Aulnay sous Bois, (also listed as Roissy), France, and in the United States through Savage Laboratories, Melville, NY (see Table 1).

**Biologic Behavior of Lipiodol**

As mentioned above, Lipiodol has been highly successful as long-term replacement therapy for iodine deficiency disease, and by 1 estimate (97) more than 60 million doses have been administered (see references 20, 35, 43). Usually 1–2 mL (480–960 mg of iodine) are given to adults. The cost per dose can be brought down to well below US $1.00 (84).

**Suggested deiodination routes**

The success of treatment with iodized oils depends on the slow, continuous release of iodide from the stored lipid over long periods of time from various pools, particularly, but not exclusively, adipose tissue (41, 88). The mechanism by which Lipiodol releases its iodine is not known. The thyroid hormone deiodinases have not, apparently, been tested with alkyl iodides or haloacids as they are presumably specialized for aromatic C-I bonds. Similarly, it is not known whether deiodinations by peroxidases, such as seen in the transiodinations catalyzed for aromatic iodides, may be involved (98). By contrast, microbial alkyl halide or fatty acid halide dehalogenases are well known to dehalogenate short-chain compounds and might work on Lipiodol. These enzymes are members of the glutathione S transferases, a multigene family that can, in bacteria, abstract halogens from a variety of organic compounds (C-I > C-Br > C-Cl as might be expected from the bond strengths) (40, 49, 96). The enzyme catalyzes the conjugation of reduced glutathione with various hydrophobic compounds that contain an electrophilic substituent. Members of this family are also present in various mammalian tissues with different tissue and substrate specificities; they can deiodinate short-chain iodoacids by displacement of the halide, most often with an enzyme-bound carboxylate, followed by hydrolysis (26). Whether or not these transferase isozymes can use iodostearic acids re-

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**TABLE 1. Composition of iodized oils**

<table>
<thead>
<tr>
<th>Product (I Content)</th>
<th>Unsat. Fatty Acids (%)</th>
<th>Source</th>
<th>Iodostearates (% of I as)</th>
<th>References &amp; Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipiodol (ultrafluide)</td>
<td>(98% unsat.)</td>
<td>Oleic (30)</td>
<td>Mono- (22) (Papaver somniferum)</td>
<td>(38) Expensive, limited supply</td>
</tr>
<tr>
<td>Ethiodol (37%-38%) (475 mg/mL)</td>
<td>Linoleic (65)</td>
<td>Di- (73) (Papaver somniferum)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Linolenic (04)</td>
<td>Tri- (15) (Papaver somniferum)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brassiodol (31.6%) (376 mg/mL)</td>
<td>Oleic &amp; Erucic (60)</td>
<td>Mono- (53) (Brassica compestis)</td>
<td>(45, 46, 52) Longer t1/2 than Lipiodol, inexpensive</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Linoleic (20)</td>
<td>Di- (27) (Brassica compestis)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Linolenic (09) (ethyl esters)</td>
<td>Tri- (15) (Brassica compestis)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yodiol</td>
<td>Oleic (56)</td>
<td>Mono-&gt; Di- (Arachis hypogaea)</td>
<td>(116) Longer I retention, Indonesia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Linoleic (26)</td>
<td>(triglyceride)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oriodol (540 mg/mL)</td>
<td>(See Lipiodol but as triglyceride)</td>
<td>Ppoy seeds (Papaver somniferum)</td>
<td>(see Lipiodol)</td>
<td></td>
</tr>
<tr>
<td>Soybean oil (37.1%) (485 mg/mL)</td>
<td>Oleic (24)</td>
<td>Mono-&gt; Mono- (Glycine soja)</td>
<td>(137) Oral and IM, 4th Pharmaceutical Co., Wuhan, China</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Linoleic (54)</td>
<td>(triglyceride)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Linolenic (07) (triglyceride)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walnut oil (38.2%) (507 mg/mL)</td>
<td>Oleic (18)</td>
<td>Mono-&gt; Mono- (Juglans regia)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Linoleic (73)</td>
<td>(triglyceride)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Linolenic (03) (triglyceride)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
piodol, the thyroid gland contained the second high-odol. This leads to a liver effective half-life of nary iodine is, in fact, the anion and not low molecu-
that only rarely has it been shown in humans that uri-
not long-lived enough. It must be pointed out again
brisk, and nearly linear, secretion of 131I in the urine
days (55). These findings were accompanied by a
appearance of iodide after oral Lipiodol may be due, in
part, to bacterial enzymes in the gut. Whether or not the gastrointestinal tissues contribute their own en-
zymes to this rapid deiodination remains to be deter-
An interesting example of rapid disposal is seen after intrahepatic artery injection of [131I]Lipi-
dol. This leads to a liver effective half-life of ~4 days
and a hepatoma half-life of ~5 days (69, 80). Al-
though patients receiving these materials tend to be
very sick, it is somewhat surprising that, despite the
fairly rapid deiodination, there are only a few reports of thyroid 131I accumulation (94). There is often not
a mention of thyroid blockade in the reports. However, after lymphatic injection of 131I-labeled Li-
piodol, the thyroid gland contained the second high-
est per gram 131I (after lung) over a period of 3–17
days (55). These findings were accompanied by a brisk, and nearly linear, secretion of 131I in the urine
amounting to 35% of the dose at 15 days. An even more rapid cumulative urinary excretion (50% of the
dose in 8 days) is seen in patients after hepatic artery injection of labeled Lipiodol for hepatoma (80). This
differs markedly from the excretion rates seen with Lipiodol administration for iodine deficiency. While it has not been proved that this radioactivity is pres-
ent as the anion, the urinary pathway suggests this.
Iodine ion has been shown chromatographically to be the major urinary iodine component in rats given Ethiodol, but a significant fraction can be contrib-
uted by organic forms (88). Intestinal disposal was found to be minimal.

Effective half-life

As mentioned above, Lipiodol administration by oral or intramuscular routes has yielded much longer half-lives and more complex patterns of iodine elimi-
nation than after intravascular administration. These measurements have to be based on chemical deter-
mination of urinary iodide excretion because 131I is not long-lived enough. It must be pointed out again
that only rarely has it been shown in humans that urin-
iode (cumulation (46). The halflife of disappearance of radioactively labeled Li-
piodol from the intramuscular injection site was much shorter (70 days) than the half-life of urinary io-
dide (5.5 months), suggesting that slower pools exist
elsewhere in the body (70). On the other hand, iodized
soybean oil could be demonstrated radiographically
at the injection site up to 3 years after injection (137),
and Ethiodol was readily demonstrated at the injec-
tion site at 6 months (25, 88).

A further complication is the frequent finding that
urinary iodide excretion is a multi-exponential func-
tion. The decline in urinary iodide values is at least bi-
exponential, with an early fast period with the time
required to decrease urinary iodine by 50% (t1/2) of ~1
week, and a slower component with a t1/2 of ~3
months or more (7). In a comparison of two different iodized oils, Ingenbleek et al (46) report that both have
bi-exponential disposal. The fast, early component is
the same for the 2 oils, whereas the second phase is
substantially slower for Brassiodol than for Lipiodol,
and is hence recommended as the more efficacious oil
to use. The early phase of iodide excretion is, not sur-
prisingly, accompanied by a rapid thyroidal iodide ac-
cumulation (~10-fold at 90 min) (88). In the guinea pig
given oral radioiodine-labeled iodized oil, there was
rapid intestinal loss of label; this depended on the gas-
trointestinal transit time and was due, in part, to deio-
dination and also possibly to poor absorption, which
did not occur after intramuscular administration (122).
Similar observations were made in the rat, where the
biologic half-life was increased from 5.5 to 30 days
upon changing from oral to intramuscular administra-
tion, and in humans, where the half-life was increased
from 25 to 76 weeks for the same dose of Lipiodol. This
difference in the route of administration has also been
observed by others (28, 85). Intramuscular Lipiodol ap-
ppears to avoid some of the extremely high early iodide
levels seen after oral administration. On the other
hand, transient, painful induration at the injection site
has been reported; whether this is due to local embolization as seen in the liver (see above) has not been determined. A review of the relative merits of oral versus intramuscular Lipiodol is available (25). Complex iodide excretion patterns are also seen after intrahepatic artery administration (80). Thilly et al (112) have separated 4 exponentials in their Ubangi (Zaire) study, although each slope is secured by only 2 points. Results from these and other studies are summarized in Table 2. It should be emphasized that these are rough estimates because of the curvature in the excretory patterns and the paucity of data points.

It is not known whether part of the excretory complexity reflects heterogeneity in the administered Lipiodol preparations (in Ethiodol 37%-38% iodine is present as 3 different iodinated fatty acid esters). The fraction of iodinated products in Lipiodol present as mono-iodostearic acid varies considerably compared to the di- and tri-iodostearic acids (see Table 1). This may well be reflected in different rates of deiodination. Preliminary results have shown that monoiodinated fatty acids are more stable in the body than di- and tri-iodinated ones and will, thus, release iodide for longer periods (118). For example, Ingenbleek et

![Diagram of Urinary Iodine Excretion Patterns](image-url)
al (45, 46) suggest that the longer half-life of Bras-
siodol may be due to the presence of iodine as iodi-
nated erucic acid (C22:1) which has a low turnover
rate from white adipose tissue; however, more data
are needed. In another example iodized peanut oil
was stated to have a longer retention time than Lipi-
odol (116). Hence the composition of the starting oil
may determine its lifetime in the body (see Table 2).
Moreover, attention should also be paid to the ques-
tion of whether or not iodized oil as oral triglyceride
versus fatty acid esters have a longer half-life in the
body (11, 35). This question has not been settled de-
finitively. Alternatively, different deiodination rates
may reflect the presence of different deiodinating
isozymes in different tissues. Finally, different body
pools may metabolize Lipiodol at different rates, for
example, Ethiodol mixed with human serum shows a
significant deiodination rate (13% in 15 hours) as well
as some binding to serum proteins (88).
A brief mention should be made regarding the pos-
sibility that Lipiodol may have a direct effect on tis-
sues not dependent on its deiodination. Besides the
effects on embolization after intravascular adminis-
tration mentioned above, Ethiodol has been found to
inhibit macrophage phagocytosis, surface electro-
negativity, and membrane microviscosity (50), and
after thyroid gland lymphography in dogs, acute and
chronic cellular infiltration in the interlobular con-
nective tissue has been demonstrated (105). It is
doubtful that these findings have important conse-
quences for prophylactic oral or intramuscular Lapi-
odol administration except at the injection site.

**Dietary and patient-related factors in the efficacy of Lipiodol treatment**

The following factors may affect the response to Lipiodol treatment:

1) Fierro-Benitez et al (33) found that in women and older children, the half-life of urinary iodine in
the malnourished was only about one-half that of the
well nourished. This was accompanied by increased
rates of urinary iodide excretion in the malnourished
group. This effect is likely to be due to both de-
creased peripheral availability of iodine from Lipi-
odol and depressed thyroid function (37).

2) A factor in the variable response to Lipiodol is
the widespread infestation of many iodine-deficient
populations with *Ascaris lumbricoides* and/or *En-
tameba histolytica*. These appear to diminish ab-
sorption or retention of Lipiodol as judged by urinary
iodide excretion. This defect is readily reversed by
appropriate treatment of the infestation (36, 116).

3) Iron deficiency anemia substantially decreases
the efficacy of iodized oil when compared with that
in nonanemic children (of the Côte d’Ivoire), and the
decrease in thyroid volume following iodized oil cor-
relates directly with the hemoglobin level (134). Sup-
plementation with ferrous sulfate restored the thy-
roid response to Lipiodol (135).

4) Poor response to Lipiodol may also occur in pa-
tients with fibrosed, long-standing goiters that retain
little functional thyroid tissue (17). This decreased
thyroid reserve is accompanied by a decreased thyro-
globulin output, and the serum thyroglobulin/thyroid-
stimulating hormone (TSH) ratio provides a good
measure of the ability of the thyroid to respond to Li-
piodol.

5) Diarrheal disease.

6) Iodine-deficient populations often use manioc
or cassava as a dietary staple. Incomplete processing
of this material, which leads to the formation of thioc-
cyanate (via cyanogenic glycosides and detoxifica-
tion of the cyanide produced from these), may lead
to competitive inhibition of iodide transport. This
will be particularly severe on a background of iodide
deficiency because thiocyanate will be a more effec-
tive competitor (20, 21, 132).

7) It has been known for some years that selenium
is somehow required for normal thyroid function. Ini-

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**TABLE 2. Approximate half-lives of urinary iodine excretion after Lipiodol administration to iodine-deficient populations**

<table>
<thead>
<tr>
<th>First Author (Reference)</th>
<th>Route</th>
<th>Urine Iodine $t_{1/2}$ (days)</th>
<th>Radiiodine $t_{1/2}$ (days)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretell (89) IM</td>
<td></td>
<td>5.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fierro-Benitez (32) IM</td>
<td></td>
<td>5.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malamos (70) IM</td>
<td></td>
<td>5.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiily (113) IM</td>
<td></td>
<td>2.2; 4.2; 13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eltom (28) IM</td>
<td></td>
<td>~4.2–4.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boukis (5) IM</td>
<td></td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ishizuki (47) Vaginally</td>
<td></td>
<td>3.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bennioud (7) Oral</td>
<td></td>
<td>(1 week); 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elnager (27) Oral</td>
<td></td>
<td>&gt;3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ingenbleek (45, 46) Oral</td>
<td></td>
<td>7.5</td>
<td></td>
<td>Lipiodol</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>~4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: IM = intramuscular; $t_{1/2}$ = time required to decrease urinary iodine by 50%.
Initially this was credited to the decrease in glutathione peroxidase, a selenium-containing enzyme that decomposes hydrogen peroxide which, in turn, was thought to protect the thyroid against excess peroxide. More recently it was found by Larsen and Berry (59) that type 1 5'-iodothyronine deiodinase contains selenocysteine in the catalytic site. Because the thiolate anion is the reactive species in most reactions involving cysteine, the better catalytic activity of selenocysteine, as compared to cysteine, can, in part, be ascribed to the much lower pK (~3 orders of magnitude) of the dissociation of R-SeH to R-Se− + H+.

Thus, in the deiodinase the selenocysteine is nearly completely dissociated at neutral pH. This enzyme converts thyroxine to the more active triiodothyronine, and selenium deficiency might, therefore, be expected to exacerbate iodine deficiency (3, 59). In fact, these 2 deficiencies coexist in many parts of the world, particularly China and Central Africa. It comes as no surprise therefore, that the efficacy of Lipiodol in reducing goiter size is markedly diminished as a function of decreased serum selenium concentration in goitrous, selenium-deficient children, for example, in the Côte d'Ivoire (136). It remains to be shown that Se supplementation will reverse the decreased efficacy of Lipiodol. Selenium requirements to satisfy the synthesis of the deiodinase are lower than for glutathione peroxidase, thus the deiodinase is the more critical enzyme. Recently it has been shown that all 3 known iodothyronine deiodinases are selenocysteine-containing proteins and may thus also be involved in diminished thyroid function during selenium deficiency, but the type 1 enzyme appears, at present, to be the more important 1 in iodine deficiency (107).

An additional consequence of the coexistence of selenium and iodine deficiencies is the occurrence of Kashin-Beck osteoarthropathy (osteonecrosis) as seen in Tibet (79). Low urinary iodine with high serum TSH levels and Se deficiency are associated with increased risk for this disease. Tests with supplementation with Se or iodine alone will be required to determine if this association is obligatory. Because this disorder has not been reported from Africa, where both trace elements are deficient, other factors may be involved.

**Side Reactions—Adult**

The massive storage and long residence time of a number of lipid soluble iodinated drugs in the body have long been known to interfere with iodine-dependent diagnostic tests and might be expected to be associated with a number of adverse reactions in the thyroid. Amiodarone is an extreme example where such side reactions have been observed frequently (reviewed in 123, 128). Considering that some 90 million doses of Lipiodol have been dispensed (97), the relative lack of side reactions that have been reported after Lipiodol is surprising (74, and below). This may be due, in part, to the considerably smaller iodide load supplied; in part to the difference in deiodination between iodinated aryl and alkyl groups; and, in part because Lipiodol is often administered under conditions where follow-up is likely to be less than optimal and side reactions may be under-reported. The following is an attempt to examine this question. In particular, will a single dose of 1–2 mL of Lipiodol (as given for endemic goiter prophylaxis) pose any significant danger of iodide side reactions to the general population on the 1 hand, and to the mother and fetus, on the other. Recently it has been proposed that somewhat smaller doses (equivalent to 200 mg of iodine) provide adequate protection for ~1 year, and it was claimed that fewer side reactions occur at the lower dose, but no data were supplied (27). However, in general, it is preferred to administer larger doses because of the longer duration of effectiveness.

**Mechanism of excess iodide effects**

Side reactions ascribable to iodide can be classed as follows: a) as acute or chronic inflammatory disease such as thyroiditis and sialadenitis caused by mechanisms not well understood; b) as excess substrate for hormone production leading to hyperthyroidism; and c) as hypothyroidism or iodide goiter for which some mechanistic ideas can be detailed.

It was initially thought that excess iodide inhibited thyroid hormone formation by competition by iodide for the active, oxidized iodinating species (the so-called Wolff-Chaikoff effect). However, it soon became apparent that a large number of other metabolic processes not directly involving thyroid hormone formation were also inhibited. These include peroxide generation, iodide transport, hormone secretion, growth of thyroid cells in culture, adenylate cyclase, glucose oxidation, lactate production, uridine and thymidine uptake, protein synthesis, amino acid transport, calcium efflux, resting potential, prostaglandin synthesis and release, and phosphatidyl inositol turnover, among others (reviewed in 25, 125, 128). More recently, it has been shown that the level of the sodium/iodide symporter, NIS, was similarly diminished by excess iodide (29, 117). This immediately offered an explanation for the temporary nature of thyroid gland inhibition by excess iodide. The best current explanation is that this effect is mediated by iodinated lipid inhibitors, described below. It seems unlikely that these effects are caused by intrinsic toxicity of Lipiodol.

Two classes of compounds have been described and found to be thyroid gland inhibitors and mediators of the effects of excess iodide. The formation of
both requires prior oxidation of iodide to a reactive form, as is the case for iodination of thyroglobulin; such iodinations do not occur in the presence of antithyroid agents such as propylthiouracil, etc. The first compounds were found to be addition products to polyunsaturated fatty acids such as arachidonic acid as shown in Figure 2. Because these iodinations occur in an aqueous phase, the products are iodohydrins, that is, 1 of the double bond carbons receives iodine while the other receives an $-\text{OH}$ (128). Furthermore, because of this $-\text{OH}$, the iodinated lipids can lactonize with the carboxyl of the fatty acid and form internal ester (lactone) rings of different sizes (see Figure 2). With multiple double bonds,
multiple iodinations and isomerism due to the location of the –I and –OH substituents (as well as cis-trans isomerism of these), hundreds of permutations are, in principle, possible. However, only a few have been found so far. There appears to be some specificity as to which derivative is most inhibitory for which function of the thyroid (23, 24, 59, 128).

Boeynaems and colleagues (83) found another iodinated inhibitor, 2-iodohexadecanal, formed from plasmalogens (vinyl ether phospholipids) present in thyroid membranes (see Figure 2). It also inhibits a number of functions in the thyroid (and in other tissues). Its specificity derives from its synthesis by the iodide oxidation system, essentially restricting the occurrence of 2-iodohexadecanal to the thyroid gland.

What factors determine the choice between lipid and protein iodination? Why isn’t there always inhibition? Or is there? Are there different thresholds of iodide for the 2 substrates? Pereira et al (83) showed that the concentration dependence for iodide was about 10-fold lower for protein iodination than for lipid iodination. This difference would fit admirably with a turn-on of inhibition by excess iodide and relatively little inhibition under normal iodide loads. It is also possible that this preference for protein iodination may be due to a lesser intrinsic reactivity of addition to an olefinic double bond in polar solvents than for aromatic substitution. Two areas that bear further investigation are the turnover of the inhibitors and, why do some people receiving the same iodide load develop iodide goiter (that is, do not adequately suppress NIS), whereas most adapt to the iodide excess? For example, can this difference be equated with the wide variations in iodide metabolism even within the same gland (1)?

### Lipiodol-induced thyrotoxicosis

Small outbreaks of iodide-induced thyrotoxicosis keep cropping up in populations recently provided with iodine replacement, generally not from Lipiodol (103), but rather after attempts to substitute iodized salt prophylaxis for Lipiodol (10, 114). Although the results are preliminary, KI appears to produce more iodide-induced thyrotoxicosis even though the initial iodide load attained in the body from Lipiodol is likely to be greater early after institution of prophylaxis. Whether this is due to the rather high levels of salt iodization, the slow later release of iodide from Lipiodol, or other factors, remains to be established. One may wonder whether the initial iodide surge after Lipiodol administration may, in fact, protect against thyrotoxicity.

In a previous report we tabulated the Lipiodol experience with respect to iodide-induced thyrotoxicosis (34; see also 103, a thorough update). This complication occurred in 14 of 11,433 subjects treated with Lipiodol for endemic goiter, rather less frequently than after iodide supplementation. Since then, an additional 40 cases have been published in larger studies (Table 3). Cases found in studies with fewer than 30 subjects are not listed (19, 61, 99). Of the 40 cases, 23 were “laboratory thyrotoxicosis” only (that is, without detectable clinical manifestations), and 6 occurred in patients with large diffuse or nodular goiters. Occasional transient and subclinical (laboratory abnormalities only) cases of hyperthyroidism have been reported (4, 5, 8, 19). In a study (68) of 240 subjects previously mentioned, the prevalence of iodide-induced thyrotoxicosis was 1.7%, an incidence much higher than observed in

### Table 3. Incidence of iodide-induced thyrotoxicosis (IIT) after non-radiographic use of iodized oil

<table>
<thead>
<tr>
<th>First Author (Ref)</th>
<th>Country</th>
<th>Cases of IIT</th>
<th>Total Tested</th>
<th>Total Treated</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>McCullagh (75)</td>
<td>New Guinea</td>
<td>0</td>
<td></td>
<td>7,034</td>
<td>L-SG excluded</td>
</tr>
<tr>
<td>Bartfield (13)</td>
<td>New Guinea</td>
<td>0</td>
<td>61</td>
<td>911</td>
<td></td>
</tr>
<tr>
<td>Delange (20)</td>
<td>Zaire</td>
<td>3</td>
<td>960</td>
<td>2,025</td>
<td>L-SG; decreased dose for older patients</td>
</tr>
<tr>
<td>Fierro-Benitez (32)</td>
<td>Ecuador</td>
<td>1</td>
<td>202</td>
<td>3 transient</td>
<td>3 multinodular goiters</td>
</tr>
<tr>
<td>Petrell (88, 89)</td>
<td>Peru</td>
<td>6</td>
<td></td>
<td></td>
<td>4 more with pre-existing Graves; Cassava diet</td>
</tr>
<tr>
<td>Watanabe (120a)</td>
<td>Argentina</td>
<td>6</td>
<td>202</td>
<td>3 transient</td>
<td>3 transient, 4 longer</td>
</tr>
<tr>
<td>Maberly (68)</td>
<td>Malaysia</td>
<td>4</td>
<td>240</td>
<td></td>
<td>High PBI</td>
</tr>
<tr>
<td>Boukis (8)</td>
<td>Greece</td>
<td>3</td>
<td>58</td>
<td></td>
<td>? contamination</td>
</tr>
<tr>
<td>Zita (137)</td>
<td>China</td>
<td>7</td>
<td>919</td>
<td></td>
<td>? contamination</td>
</tr>
<tr>
<td>Eltom (85)</td>
<td>Sudan</td>
<td>1</td>
<td>979</td>
<td>2,316</td>
<td>Large diffuse goiter</td>
</tr>
<tr>
<td>Martins (73)</td>
<td>Brazil</td>
<td>13</td>
<td>1,663</td>
<td>Lab. only</td>
<td>Large grade III goiters; 4 transient, 4 longer</td>
</tr>
<tr>
<td>Tonglet (115)</td>
<td>Zaire</td>
<td>1</td>
<td>75</td>
<td>1,083</td>
<td>Low dose; large nodular goiter</td>
</tr>
<tr>
<td>Elhager (27)</td>
<td>Sudan</td>
<td>4</td>
<td>107</td>
<td>1,802</td>
<td>Lab. only, transient</td>
</tr>
<tr>
<td>Azizi (4, 5)</td>
<td>Iran</td>
<td>10</td>
<td>107</td>
<td>228</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: L-SG = long-standing goiter.
other studies. Because a number of these patients showed eye signs, it seems likely that the incidence was inflated by the presence of latent Graves disease made toxic by the new iodide supply. Whether this unusual outcome is due to the intermittent high consumption of cassava forming a highly stimulated thyroid gland, the intravenous use of "Lipiodol Viscous," or other factors is not clear. In another study, high PBI values were measured 1 month after administration of 2 mL of iodized soybean oil (197), but it is not known whether potential contamination of the test by Lipiodol may have occurred. Subclinical hyperthyroidism may be accompanied by atrial fibrillation in the few cases of Lipiodol-induced subclinical hyperthyroidism. This has not been reported, but may have been missed under "field" conditions because even clinical cases are often mild. Cardiac complications appear to be more common after KI supplementation (25a).

Not tabulated here are the many studies for which no iodide-induced thyrotoxicosis was reported (for example, 13, 16, 20, 21, 42, 75, 115), and which constitute the bulk of the treated populations. It is not clear whether laboratory or frank thyrotoxicosis might have been missed under the less than ideal field conditions, especially since the disorder tends to be self-limited. Moreover, in some studies there was a degree of patient selection, for example, exclusion of subjects with very large goiters. Hence an accurate incidence cannot be calculated. Nevertheless, on the basis of the vast number of doses given (97), it seems reasonable to deduce that the incidence of clinically significant Lipiodol-induced thyrotoxicity is likely to be <0.1%. It should also be noted that the reported incidence of iodide-induced thyrotoxicosis from all iodide sources decreases as an inverse function of the sample size (127).

We have previously speculated on the mechanism by which iodide may induce thyrotoxicosis (34). In addition to the obvious situation in large multinodular goiters which are likely to contain autonomous tissue hungry for iodide, one could postulate unsuspected foci of autonomy in smaller, non-nodular goiters; an attractive hypothesis—all that is needed is proof. The normal thyroid eventually senses the presence of excess iodide and responds by reducing iodide transport through inhibition of the Na/I symporter (NIS) synthesis (and the bulk of other metabolic processes in the gland) (29, 116). Apparently this results from the formation of iodinated lipid inhibitors. The threshold for such regulation may be much higher in some individuals who will eventually become thyrotoxic. Thus a defect in autoregulation is probable but not proved. It is well known that large multinodular goiters may contain enough autonomous tissue to make them more susceptible to iodide excess. A number of groups have excluded such patients from Lipiodol administration (see Table 3). This susceptibility has been ascribed to TSH receptor mutations that lead to constitutive activation (18). The mutation rate may be increased by the oxidizing/iodinating environment in the thyroid. This would ultimately lead to uncontrolled thyroid hormone secretion as soon as iodide is supplied. Whether this is the only locus for autonomy is not known. Latent Graves disease may be similarly sensitive; there are, however, few cases of the latter on record (68).

The striking rarity of side reactions to Lipiodol prevents an accurate assessment of all of the aspects of Lipiodol-induced thyrotoxicosis. From the few cases that have been observed, it appears that the clinical picture does not differ significantly from that seen with other forms of iodide-induced thyrotoxicosis (34). The differences from Graves disease include the following: the sex ratio of female/male is ≤1.0; there are no significant antibody elevations; there are no eye signs (unless preexisting latent thyrotoxicosis was present); radioactive iodine uptake is usually low when iodide loads are high; urinary iodide levels are high (depending somewhat on the time after Lipiodol administration). The toxicity is usually self-limited with complete resolution, but symptoms may last a year. In the case of Lipiodol the long half-life of the oil may increase the duration but it is unlikely to be as long as seen after amiodarone therapy (129). Lessons from amiodarone-induced thyrotoxicity suggest that when symptoms are severe enough to require therapy, potassium perchlorate with or without a thionamide should be considered (129). To what extent this is feasible in remote areas remains to be seen since these agents have their own complications.

**Sialadenitis**

It has been known for a long time that tissues other than the thyroid, such as mammary tissue, salivary glands, gastric mucosa, choroids plexus, etc., concentrate iodide by a mechanism similar to that of thyroid tissue (for example, 131). The $K_m$ for iodide is the same, but the accumulation in salivary or mammary tissue, for example, is less, in part because these tissues have an open duct system, whereas the thyroid follicle might be considered a closed duct with consequent greater accumulation. These tissues have now been found to have the same or very similar syporter (NIS) (102), whose absence has a global effect on all iodide-concentrating tissues, as could be expected from early work (126). Excess iodide might thus affect the salivary gland and cause iodide-induced sialadenitis, or iodide mumps. It is occasionally seen after excess KI in both submaxillary and parotid glands, but is rare after iodized oil. In 1 study with 238 women and children, a surprising finding was a 24% incidence of transient sialadenitis after administration of 2 mL of Lipiodol (86). In another study (28), 3.5% of subjects...
are stated to have experienced transient sialadenitis. No such findings are recorded in most other studies.

**Thyroiditis**

Despite the still controversial belief that thyroiditis may be correlated with chronically increased iodine intake, the overwhelming number of subjects treated with Lipiodol show no significant changes in their antithyroid antibody titers (for example, 28, 53, 60). Isolated examples exist, but often no pre-Lipiodol controls were made. Increased titers have been reported from Greece (8) and after hysterosalpingography (employing 10 mL of Lipiodol) in Japan (48). There are also rare reports of acute painful thyroiditis (22, 47) after high doses, but this is extremely rare. For chronic thyroiditis one may speculate that if iodide has the potential to cause autoimmune thyroid disease in these populations, then it may require much longer follow-up periods than have so far been used because changes in antibody titers are almost never reported (120).

**Iodide goiter and/or hypothyroidism**

Long-term inhibition of the thyroid by excess iodide is generally overcome by autoregulation of iodide transport (12, 29, 130). Many metabolic pathways of the gland are reduced (24, 128), but for self-protection the decrease in the Na/I symporter (NIS) (both messenger RNA and protein) plays the major role (29, 117). The net effect of these changes is to reduce iodide transport into the gland and, hence, leads to protection against excess iodide. The general postulate (not proved in the clinical situation) is that down regulation of NIS fails to occur in selected individuals leading to eventual hypothyroidism, goiter or both, as shown, for example, with seaweed goiter in Hokkaido (76, 124). Although the precise dose of iodide needed to induce iodide goiter is variable, this complication generally requires larger doses of iodide and longer exposure than for induction of thyrotoxicosis. Furthermore, we know from the amiodarone experience that iodine-deficient populations exposed to the drug are more likely to experience thyrotoxicosis, whereas iodide-sufficient populations are prone to iodide goiter (123, 129). To attain inhibitory concentrations, say 20-fold the daily requirement, is considerably more difficult with a single dose of Lipiodol than providing extra iodine for induction of hyperthyroidism. Moreover, to produce goiter or clinical hypothyroidism takes time, although increased serum TSH levels may occur early (see below). Compare this with the estimate by Léger et al (61) that in France a plasma iodide level 10 times higher than normal sufficed to initiate thyrotoxicosis in some of the population. Note that these limits serve as a guide for evaluating untoward reactions to Lipiodol therapy and are in no way accurate.

While reports of iodide goiter continue to appear, in most of these the culprits appear to be KI or amiodarone. Lipiodol, when used as a radiographic contrast medium (that is, larger doses delivered into the vasculature or body cavities), can cause fetal goiter and/or hypothyroidism. A case using only 4 mL of Lipiodol for lymphography illustrates the need for considering thyroid complications (41). A 15-year-old boy underwent bipedal lymphography with 4 mL of Lipiodol Ultrafluide to exclude metastases from a resected histiocytoma. No metastases were found but 3 weeks later the TSH level was 42 μU/mL with normal T4 and T3 levels. By 6 weeks the patient had developed a grade II goiter with a 1-cm nodule in the right lobe. He was clinically mildly hypothyroid with a TSH level of 27 μU/mL, T4 of 2.8 μg/100 mL, and normal T3 levels. Antithyroid antibodies were undetectable; urinary iodine excretion was 18 mg/24 h. Treatment with L-thyroxine (dose not stated) for 3 months returned hormone levels to normal and the goiter and nodule disappeared. L-thyroxine was discontinued and thyroid status remained normal despite persistently high urinary iodide level of 2.5 mg/24 h at 7 months. The case for long-term thyroid follow-up is well illustrated. By contrast, Lipiodol, as used for supplementation, has not led to the development of iodide goiter. However, transient and mild subclinical hypothyroidism is occasionally seen early after iodized oil administration when very high urinary iodide excretion occurs (45, 46). In Nepal, 8 subjects had transiently increased TSH and decreased T4 levels (19). Detection of this complication probably requires a detailed time course of laboratory measurements and may have been missed in some studies. One should note the difficulty of detecting iodide goiter under field conditions in areas of highly prevalent iodine-deficient goiters.

**Side Reactions—Fetus and Neonate**

The great vulnerability of the fetal thyroid to excess iodide is well demonstrated by the appearance of goiter of the newborn (often with hypothyroidism) following administration of iodine-containing drugs to pregnant women (123, 124). Moreover, a single dose of 15 mg KI given for radiation protection to 3,214 newborns in Poland during the Chernobyl accident (82) led to 12 cases of transient increases in TSH and decreased T4 levels. The effect was normalized by 2–3 weeks; a 2-year follow-up revealed no signs of permanent damage. These observations prompt a reexamination of this population after exposure to Lipiodol.

We must ask several questions about the mechanism of iodide generation leading to these possible undesirable side effects in the fetus or neonate:
1) What concentrations of circulating iodide are attained in the mother and what is the time during which iodide levels are in the inhibitory range?

2) How does the maternal iodide level relate to that of the fetus? Is there simple diffusion across the huge surface area of the placenta, or is there active transport from mother to fetus?

3) How common is fetal iodide goiter after Lipiodol, are there other side reactions, and is there a reliable denominator? At what stage of gestation must we worry about the effects of excess iodide, and when does autoregulation start in the fetal thyroid? What is the inhibitory iodide concentration in the fetus?

4) What are the iodine contributions from breast milk? Available data to answer most of these questions are scarce or soft, and what follows is, at best, a framework for further studies.

**Maternal iodide concentrations**

Plasma iodide levels in normal pregnant women show considerable variation but appear to vary from 0.1–0.3 μM, a value not significantly influenced by the pregnancy itself in areas that are iodine sufficient (63). Presumably these values will be lower in iodine-deficient areas. As mentioned above, Lipiodol in a 2-mL dose delivers ~950 ng of total iodine to the patient; the bulk of this iodine finds its way into lipid or other storage depots where it enjoys a very long half-life, releasing iodide slowly and maintaining urinary iodide above starting levels for a year or more. What do urinary iodide levels tell us with respect to the blood iodide levels which, in turn, control thyroid iodide levels? Such calculations appear not to have been made for replacement therapy with iodized oil. Early observations (121) showed a nearly, but not perfectly, linear relation between urinary and plasma iodide levels at low iodide loads such that for every 50 μg/24 h increase in urinary iodide, there is an increase of 0.25 μg/100 mL in plasma inorganic iodide. Thus, at 200 μg urinary iodide/24 h, the circulating iodide level would be 10 μg/L, or just under 0.1 μM in the circulation, a level at the low end for pregnant women and well below those at which inhibitory effects of iodide on the thyroid are measurable. Whether the relation between urine and plasma iodide levels remains the same at the higher iodide loads seen early after Lipiodol administration remains to be determined. Recalculation of recent data (71) suggests that plasma iodide concentration as a function of urinary iodide output falls off at high loads.

The minimum inhibitory level of circulating iodide for thyroid function depends on the activity of the gland; in the thyrotoxic adult thyroid it is ≥5 μg/100 mL or ≥0.4 μM, but is higher in normal, unstimulated human thyroids (104, 124). Because the iodine-deficient gland may be presumed to be very active, this appears to be a reasonable threshold value to use in considering the effective concentrations of iodide that the Lipiodol must deliver to the mother’s circulation. The value is likely to be higher in populations consuming significant quantities of manioc (cassava) because a high blood level of the transport competitor, thiocyanate, is often found (9, 91); in addition, thiocyanate can inhibit the oxidation of iodide (2). The iodide surges early after Lipiodol administration might be expected to exceed such circulating iodide levels. However, the paucity of thyrotoxic cases (see above) suggests either that higher iodide threshold values obtain or that there is an efficient Wolff-Chaikoff mechanism against iodide excess in these active glands.

**Fetal iodide concentrations**

What do maternal iodide levels mean for the fetus? While the large surface area of the placenta would provide efficient diffusion of iodide to the fetus, there are animal experiments that show that the placenats of guinea pig, rabbit, and sheep exhibit active transport of iodide from the mother to the fetus that shows saturation and competition with thiocyanate. Concentration ratios vary from 2–9 in favor of the fetus of experimental animals pari passu with placental development (11, 14, 39, 55, 66, 81). Similar data obviously cannot be obtained for the human placenta; however, since both guinea pig and human placentas are of the hemochorial type, it may be reasonably supposed that some active transport of iodide across the human placenta can occur. Of great interest in this discussion is the finding that both faces of the placenta have been shown to contain NIS (N. Carrasco, personal communication).

Since the placenta is highly permeable to iodide, the delivery to the fetus will directly reflect the maternal level. The question is: will the early iodide surges have adverse effects in the fetus? In a recent study in rabbits using 125I-labeled iodized oils (11), label was rapidly incorporated by both the maternal and fetal thyroids: oral Oriodol > oral Lipiodol > intramuscular Lipiodol (see Table 1) over a period of 15–28 days. Moreover, the placenta/plasma concentration was >1. Assuming a conservative concentration gradient of 2, the minimum required maternal urinary 24 h iodide output would be ~5 mg/day to put the fetal thyroid at risk if the fetal thyroid behaved like that of the mother. Note that the mean normal amniotic fluid iodide concentration is 7.8 μg/ liter; this concentration of iodide increases markedly when the mother has received rapidly metabolized iodinated contrast media (31), but no information on Lipiodol-derived iodide is available. Other factors may influence such an estimate. One of these is the possible interference of thiocyanate from manioc.
Development of fetal risk

When during gestation is the fetus at risk for excess iodide? The onset of function in the fetal thyroid occurs at 10–14 weeks of gestation, roughly as the follicular structure develops. It is not certain at present whether the onset of iodide trapping precedes organification. One would predict that NIS becomes detectable at about the same stage of development, but this has not yet been tested directly. This is also the time when the fetal thyroid approaches the mature ratio of thyroid weight to body weight (87, 100, 133). The full capacity to metabolize iodide (on a per gram basis) is not attained until halfway through gestation or later. It has been noted that the rabbit fetal thyroid concentrates iodide more efficiently than its mother (90). The thyroid of the fetal macaque accumulates 10 times as much radioiodine per gram of tissue from the mother as does the mother’s thyroid (87). This is not known to be the case for the human fetus, but the potential for damage by excess iodide in the fetus must always be kept in mind.

Autoregulation: An additional question to be answered is the age of onset of autoregulation in the fetal thyroid. As discussed above, this mechanism for combating the effects of an iodide load is very important in the adult (12, 130) and may be presumed to be similarly important in the fetus. Two animal studies by Sherwin are pertinent. The fetal cat and rabbit both lack a mechanism for limiting iodide transport after a previous exposure to excess iodide (90, 101). Importantly, premature infants exposed to povidone iodine at the time of delivery cannot protect their thyroids against the excess iodide (as shown by decreased serum thyroxine and increased TSH levels) until they are >34 weeks of gestational age (15). In newborn rats, fully functional adaptation to excess iodide takes 2–3 weeks to develop (111). It will be important to follow the development of autoregulation by assay of NIS messenger RNA and/or protein. A presumptive conclusion, that autoregulation is delayed in the fetal thyroid, seems justified. This delay in autoregulation, the increased iodide transport capacity of the fetal thyroid, and the possibility of an enhanced plasma iodide level in the fetus because of active placental iodide transport, would all be expected to increase untoward iodide effects in the fetus. The conservative approach would be to assume high sensitivity of the fetal thyroid to excess iodide and inadequate protective mechanisms against it.

One might, therefore, expect the fetal gland to become toxic. It is, however, difficult to diagnose transient in utero thyrotoxicosis, and such cases may be missed unless persistent to term. In some populations this untoward effect may have been prevented by the simultaneous presence of thiocyanate, which not only competes for iodide transport, but also blocks iodination reaction. In the immature thyroid such an effect may be more severe (2, 91).

Iodide goiter

After amniography: The other major side reaction, iodide goiter, is not infrequently seen after Lipiodol is given for radiographic purposes. Many case reports warn that goiters are seen not infrequently after “direct” fetal contact with Lipiodol during amniography, where much larger doses of Lipiodol are used than for iodine supplementation (see below). The vernix caseosa accumulates the iodinated lipid and the fetus may imbibe Lipiodol after amniography thus acquiring its own depot of Lipiodol (56, 61, 64, 72, 77, 92, 108). Goiter and/or hypothyroidism may appear within 3 weeks after (92, 95, 109, 110), and at delivery respiratory distress due to goiter continues to be reported. In a review by Stubbie (109), 30 of 62 newborns that had undergone amniofetography with Lipiodol showed thyroid abnormalities consistent with hypothyroidism; and, where histopathology was available, intense stimulation of the gland was observed. High 24 h urinary iodine output in these newborns were recorded in a number of cases, thus the fetus can deiodinate Lipiodol. However, because of the dose used and the “direct” application of Lipiodol to the fetus, these examples have little to do with the smaller doses of Lipiodol given to the mother for endemic goiter.

What about the indirect exposure of the fetus to radiographic Lipiodol given to the mother for lymphography or bronchography? Both hyperthyroidism (106) and hypothyroidism/iodide goiter (41, 47, 98, 106, 119) have been reported. Again, the quantities used exceed those for iodine deficiency. On the other hand, treatment of 35 mildly thyrotoxic pregnant women with 6–40 mg iodide/day showed no evidence of hypothyroidism in cord blood at delivery (78) even though the neonates had lower free thyroxine levels than their thyrotoxic mothers. Finally, amiodarone treatment during pregnancy has been shown to produce both hyperthyroid and hypothyroid complications in the fetus or neonate (reviewed by Wiersinga 123).

After Lipiodol prophylaxis: Is there fetal or congenital goiter after 1–2 mL of Lipiodol given to the pregnant mother? As mentioned above, in neonates given a single dose of 15 mg KI for radiation protection after the Chernobyl accident, 12 of 3,214 subjects developed transient chemical hypothyroidism that subsided after a few weeks, and left no demonstrable
sequelae at 2 years (82). With regard to Lipiodol however, neither the fetus nor the mother showed goiter or hypothyroidism in 554 pregnant patients following 0.5 mL of maternal Lipiodol, yet there were 2 neonatal goiters in 982 untreated controls. In another example, no iodide goiters were found in 452 neonates whose mothers received Lipiodol (for example, 16, 20, 21, 113). Note also that in a review of Lipiodol administration to pregnant women for iodine deficiency, Delange (21) found no examples of iodine-induced hypothyroidism. As expected, such treatment prevented both neonatal hypothyroidism and cretinism. One frequently quoted report (54) claiming a high incidence of neonatal hypothyroidism after Lipiodol has been criticized, based on the finding that the same incidence of neonatal hypothyroidism occurred in the absence of treatment. The vast preponderance of studies does not find this effect of Lipiodol. A long-term follow-up of children, now aged 11 or 15 years, of mothers who had received Lipiodol during pregnancy showed no difference in motor or cognitive function compared with children from untreated mothers (85).

To get a better grasp of the global significance of possible iodide goiter let us do the following “gedanken” experiment. Let us say that 1 million patients have been treated. Approximately half of these will be women, and if we assume that 10% were pregnant at the time of Lipiodol administration, we are dealing with 1 million patients in 982 untreated controls. In another example, no iodide-induced goiters were found in 452 neonates whose mothers received Lipiodol (for example, 16, 20, 21, 113). Note also that in a review of Lipiodol administration to pregnant women for iodine deficiency, Delange (21) found no examples of iodine-induced hypothyroidism. As expected, such treatment prevented both neonatal hypothyroidism and cretinism. One frequently quoted report (54) claiming a high incidence of neonatal hypothyroidism after Lipiodol has been criticized, based on the finding that the same incidence of neonatal hypothyroidism occurred in the absence of treatment. The vast preponderance of studies does not find this effect of Lipiodol. A long-term follow-up of children, now aged 11 or 15 years, of mothers who had received Lipiodol during pregnancy showed no difference in motor or cognitive function compared with children from untreated mothers (85).

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Breast milk iodide

Finally, one must examine the contribution of iodide from breast milk in mothers who have received Lipiodol. In the study by Bourrinet et al (11) in rabbits, substantial iodine secretion into the milk occurred early after iodized oil was given with Oriodol > oral Lipiodol > intramuscular Lipiodol. Secretion of iodine from Lipiodol in lactating women has been shown to continue for 6 months after administration (16). While the nature of the iodine was not chemically identified, it is important to point out that mammary tissue contains NIS, which is involved in the delivery of iodide into the milk. It thus seems probable that the infant will be exposed to considerable iodide ion from Lipiodol-treated mothers. The iodine content of breast milk from Lipiodol-injected mothers (2 mL) was measured at 9.7 μg per 100 mL at the nineteenth month of treatment. This is more than tenfold greater than in untreated mothers (89). Whether this is enough for the infant, or requires supplementation, is difficult to judge; it would probably be wise to supplement. It is also important to point out that breast-feeding by Lipiodol-treated mothers prevents goiter in the newborn, which reappears upon cessation of breast-feeding (120). Iodide in breast milk from Lipiodol-treated mothers is thus not likely to lead to side reactions, but is likely to be beneficial.

Conclusions

1) The main conclusion, already arrived at by many others, is that the side reactions occurring from the use of Lipiodol or related iodized oils for iodine deficiency are so rare when compared to the number of doses given, as to pose no significant obstacle to its continued use. General nutrition, including protein-calorie malnutrition, selenium and iron, protozoan infestations, poisons in the diet, and loss of functional thyroid tissue are factors that must be taken into account in evaluating effectiveness of iodized oils, and should be corrected where possible. Adverse reactions with iodized oil are apparently less common than with the usual suspects such as high doses of KI, amiodarone, povidone iodine, and certain iodinated contrast media.

2) Transient, mostly laboratory, effects of excess iodide leading to increased or decreased hormone production (and the opposite behavior of TSH) are sometimes observed both in adults and in children. The fetus is well supplied with iodide from the Lipiodol-treated mother and transports it well into the thyroid, but autoregulation develops very late in fetal life. As a consequence, the fetus is potentially at risk for the effects of excess iodide. Nevertheless, these complications are rare and have not been associated with measurable permanent effects. Lipiodol treatment early during pregnancy or before will be maximally efficient and probably safer regarding side effects than administration during later pregnancy or after. The toxic effects of Lipiodol not related to its deiodination probably do not occur except possibly from embolization at the injection site.

3) When large, long-standing, multinodular goiters are prevalent in a population, a greater danger of iodide-induced thyrotoxicosis may be expected. Such subjects should be observed and/or treated carefully, but this complication should not deprive all others of the substantial benefits obtained by Lipiodol.

4) It appears to take about 10 times as high an iodide level to iodinate unsaturated fatty acids than protein, hence iodide levels required to induce hypothyroidism (by formation of iodolipid inhibitors of thyroid func-
complications resulting from excess iodide such as thyrotoxicosis, thyroiditis, sialadenitis, or hypothyroidism are much rarer after iodine supplementation with Lipiodol than with KI. They do not militate against its widespread use in endemic goiter populations, especially in pregnant women. However, patients with multinodular goiter should not be treated or should be treated only under careful observation. When Lipiodol-induced thyrotoxicosis occurs it tends to be mild or even subclinical and self-limited. If treatment is required, potassium perchlorate with or without thionamides is recommended. Iodide goiter has not been seen after Lipiodol supplementation, nor has thyroiditis. Sialadenitis occurs rarely. Iodide derived from Lipiodol readily enters the fetus, possibly by active transport, and theoretically endangers the fetus because autoregulation of the fetal thyroid occurs late during gestation. Despite the difficulty in distinguishing iodide goiter from iodide deficiency goiter of the newborn, no cases of neonatal iodide goiter have been reported. Possible mechanisms of thyroid inhibition by excess iodide are briefly discussed. The use of locally produced iodized plant oils is recommended for financial reasons as well as for the benefits derived from local participation.

Summary

Thyroid complications resulting from excess iodide such as thyrotoxicosis, thyroiditis, sialadenitis, or hypothyroidism are much rarer after iodine supplementation with Lipiodol than with KI. They do not militate against its widespread use in endemic goiter populations, especially in pregnant women. However, patients with multinodular goiter should not be treated or should be treated only under careful observation. When Lipiodol-induced thyrotoxicosis occurs it tends to be mild or even subclinical and self-limited. If treatment is required, potassium perchlorate with or without thionamides is recommended. Iodide goiter has not been seen after Lipiodol supplementation, nor has thyroiditis. Sialadenitis occurs rarely. Iodide derived from Lipiodol readily enters the fetus, possibly by active transport, and theoretically endangers the fetus because autoregulation of the fetal thyroid occurs late during gestation. Despite the difficulty in distinguishing iodide goiter from iodide deficiency goiter of the newborn, no cases of neonatal iodide goiter have been reported. Possible mechanisms of thyroid inhibition by excess iodide are briefly discussed. The use of locally produced iodized plant oils is recommended for financial reasons as well as for the benefits derived from local participation.

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