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Pulmonary Oil Deposition in Patients Subjected to Lymphography:

Detection by Thoracic Photoscan and Sputum Examination

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ABSTRACT

During clinical trials of intralymphatic therapy with radioiodinated ethiodized oil (Lipiodol Ultra-Fluid; Ethiodol) [LUF-I^{131}] for malignant disease involving lymph nodes, significant pulmonary deposition of radioactive material was demonstrated by thoracic scan in each of five cases treated. Radioactivity was detected in sputum obtained from two cases. Induced sputum specimens were subsequently obtained from patients undergoing lymphography. Fat demonstrated in sputum was confirmed as Lipiodol in one of six patients tested. Sputum examination and use of tracer doses of LUF-I^{131} plus photoscanning are suggested as sensitive methods of assessing the incidence of oil deposition in the lungs of patients undergoing lymphography. Despite limitation of the volume of oil injected, monitoring of the infusion, and absence of radiographic evidence of contrast medium in the lungs, some degree of pulmonary oil deposition appears to be an inevitable result of lymphography. Further study of lung dosimetry is being undertaken by the authors before clinical usage of endolymphatic radioisotope therapy is expanded.

SOMMAIRE

Au cours d'essais cliniques d'un traitement intralymphatique utilisant de l'huile avec radio-isotope iodé (Lipiodol Ultra-Fluide; Ethiodol) [LUF-I^{131}] et destiné à traiter une affection maligne intéressant des ganglions lymphatiques, on a pu déceler, dans les cinq cas traités, par photocartographie, de notables dépôts de substance radioactive dans les poumons. Dans deux cas, on a décelé la radio-activité dans les crachats. On a, par le suite, obtenu des spécimens de crachats provoqués chez des malades subissant une lymphographie. L'huile a été décelée comme Lipiodol, par la méthode histologique, dans les expectorations d'un des six malades. On considère comme des méthodes très sensibles l'examen des crachats, l'emploi de doses marqués de LUF-I^{131} et de photocartographie, pour évaluer les dépôts d'huile dans les poumons de malades soumis à la lymphographie. Même si on réduit au minimum le volume de l'huile injectée, si on surveille attentivement la perfusion, et même si les radiographies pulmonaires sont négatives du point de vue de la présence de substance contraste dans les poumons, il semble inévitable que la lymphographie donne lieu à un certain degré de dépôt pulmonaire d'huile. Les auteurs étudient actuellement de nouvelles méthodes de dosimétrie pulmonaire avant d'étendre davantage l'emploi du traitement intralymphatique aux radio-isotopes.

DURING the past 10 years lymphography has been increasingly widely performed. It has been found useful as a diagnostic aid[1-6] and has been recognized as a means for increasing knowledge of the anatomy and physiology of the lymphatic system.[3, 7, 8] Lymphographic techniques have been investigated as a method of directing treatment to malignant disease of lymph nodes, and in some centres intralymphatic therapy has been employed clinically as adjunctive treatment in the management of lymphoma and metastases to lymph nodes.[9-12]

The most satisfactory and most widely used material for diagnostic lymphography is iodinated poppy seed oil of low viscosity.‡ A radioiodinated version of the same material has been used for intralymphatic therapy; this of course has all the diagnostic properties of the non-radioactive oil.

The major lymph channels of the body terminate in the great veins of the neck. Material injected intralymphatically may reach the blood stream not only by this route but also through lymphovenous communications. Direct communications between lymph nodes and veins had previously been demonstrated in the living dog.[14] Increasing indirect and direct evidence of the existence and significance of lymphovenous communications in animals and man has been an important by-product of lymphography.[15-17]

CLINICAL EXPERIENCE

In the Allan Blair Memorial Clinic, Regina, lymphography has been used as a diagnostic aid in the investigation of patients with malignant disease since November 1964, and has been useful in

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‡Lipiodol "F" Fluid (Laboratoire André Guerbet, Paris), supplied by Bell-Craig Pharmaceuticals, Toronto, Ont.

TABLE I.

Patient and case No.	Age	Sex	Diagnosis	Procedure	Injection site	Volume of oil (c.c.) LUF	Volume of oil (c.c.) LUF-I^{131}	Volume of oil (c.c.) Total	Concentration of LUF-I^{131} sample (mc./c.c.)	Dose of radioactivity (mc.)	Lymphatic obstruction	Pulmonary scan	Sputum Radioactivity	Sputum Fat
E.L. 1	54	F	Metastatic melanoma	Bilateral lower limb injection	L. foot	5.0	—	10	4.2	12.6	Absent	+	NT	NT
					R. foot	2.0	3.0							
			Metastatic melanoma—second treatment	Unilateral lower limb injection	L. foot	1.5	3.5	5.0	4.3	15.0	Absent	+	+	+
W.S. 2	63	M	Lympho-sarcoma	Bilateral lower limb injection	L. foot	6.0	—	12	3.6	14.4	Present	+	NT	NT
					R. foot	2.0	4.0							
R.P. 3	54	F	Metastatic ca. breast	Unilateral upper limb injection	R. hand	2.5	—	4.25	4.0	5.0	Present	+	+	NT
					R. ante-cubital fossa	0.5	1.25							
M.P. 4	50	F	Regional recurrence melanoma of arm	Unilateral upper limb injection	R. hand	0.5	2.5	3.0	3.7	9.3	Present	+	NT	NT

NT = Not tested.

assessing the need for and results of conventional treatment by radiotherapy and surgery.

The technique used has been based on that described by Dolan and Moore,[18] using Lipiodol Ultra-Fluid (LUF) as the contrast medium and a simple gravity injection apparatus. Lymphatics have been cannulated with No. 27 or No. 30 gauge needles attached to a syringe by polyethylene tubing. With a pressure of 9.5 lb. on the syringe, the injection flow rate with our apparatus is of the order of 0.1 c.c./min. through the larger needle, but this varies with room temperature.

By the summer of 1965 sufficient experience had been gained with the technique of cannulation and injection to start using intralymphatic radioiodinated Lipiodol Ultra-Fluid (LUF-I^{131}*) on a trial basis, to assess its therapeutic usefulness in our hands, in selected cases. We were well aware of the need to minimize the danger of pulmonary oil embolism by limiting the volumes of oil injected, although in our previous cases, using non-radioactive oil, no radiopaque material had been seen on chest radiographs, taken in every case on completion of the procedure and repeated 24 hours later. To date we have not encountered radiographic signs of pulmonary embolism or significant respiratory symptoms in our 35 cases, including one patient in whom 4 c.c. of oil was accidentally injected directly into a small venule in the foot.

Our experience with the first four patients in whom radioactive lipiodol was used is described in order to record and discuss the significance of pulmonary photoscans, and of sputum examination, in patients who have undergone lymphography.

CASE REPORTS (Table I)

CASE 1

E.L., a 54-year-old white woman, had wide local excision of a melanoma of the intergluteal fold and two months later developed clinical evidence of metastasis, apparently confined to one right inguinal node. Investigation revealed no other evidence of disease. Evidently she was a candidate for radical groin dissection. A bilateral lower limb lymphogram was performed. On the clinically negative left side 5.0 c.c. of plain LUF was infused. On the clinically positive side 2.0 c.c. of plain LUF was injected and, after preliminary radiographs of the limb had confirmed satisfactory intralymphatic infusion, the injection was completed on this side with 3.0 c.c. of LUF-I^{131}. Immediately following the injection, photoscanning showed uptake of radioactive material in the right femoral, iliac and para-aortic node regions. At that time significant pulmonary oil deposition was not expected and a routine chest radiograph showed no evidence of it. On the fifth day the neck was scanned to check the thyroid and no uptake was found there, but considerable activity was coming from the lung apices. Examination of the whole thorax by the Magnascanner then produced a clearly defined pulmonary photoscan (Fig. 1).

There was no residual radioactivity in the lung immediately prior to her next intralymphatic dose (described below), which was given 49 days later.

Second treatment.—At operation, preliminary laparotomy showed no disease in the liver, para-aortic nodes (biopsy) or elsewhere above the pelvis. The abdomen was closed and right radical femoro-inguino-iliac node dissection was performed. The presence of metastatic melanoma was confirmed histologically in femoral and iliac nodes. The left groin was still clinically negative but the previous diagnostic lymphogram on this side had suggested that metastases were in fact present.

Staged radical groin dissection on the second side was therefore advised. Preoperative intralymphatic therapy was again undertaken with the twin aims of possibly destroying tumour emboli in lymphatic channels and possibly exerting a therapeutic effect on any very small metastatic deposits which might exist in nodes beyond the margins of the operative field. A second lymphatic cannulation was achieved proximal to the previous site in the left foot and 1.5 c.c. of plain LUF, followed by 3.5 c.c. LUF-I^{131}, was injected. The progress of the infusion was monitored.

*Ethiodol-131 (Abbott).

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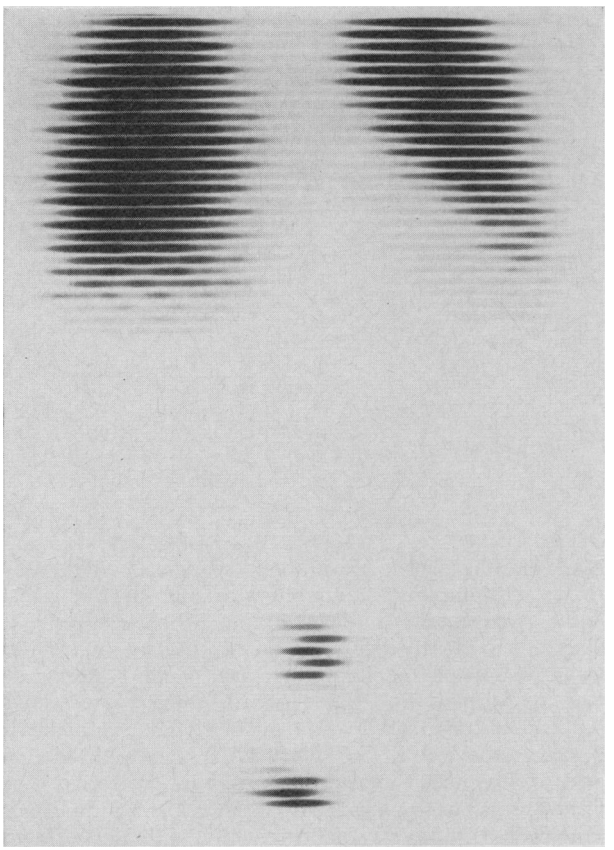

Fig. 1.—Case E.L. Composite photoscan of thorax and upper abdomen showing uptake of radioactivity in upper para-aortic lymph nodes and in lungs.

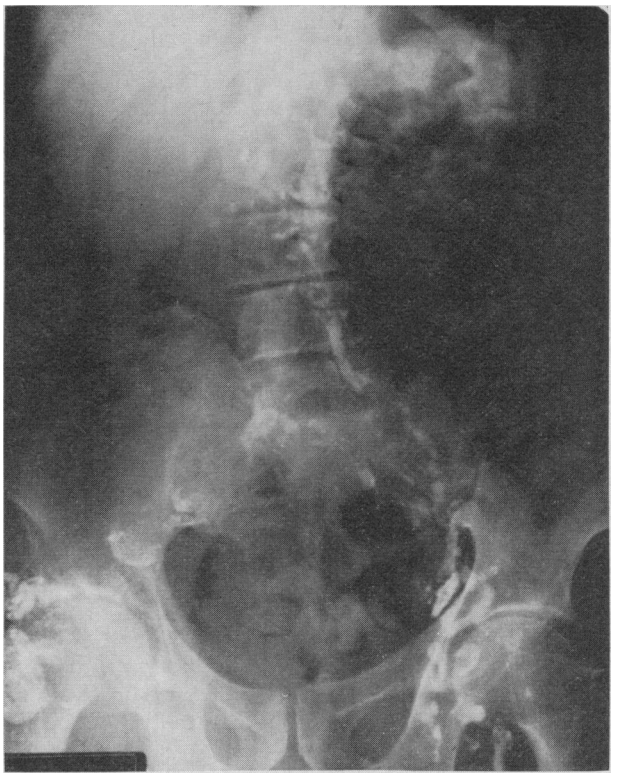

Fig. 2.—Case W.S. Radiograph of abdomen and pelvis. Lymph nodes delineated by contrast material to para-aortic level on left side. Right para-aortic and upper iliac nodes not visualized.

The foot-groin circulation time was approximately four minutes. The injection was stopped after 40 minutes because radioactivity was detectable over the abdomen above the umbilicus. No uptake of radioactivity was detectable in the lungs at the end of the infusion. The patient was moved to another room where scanning of the left groin, pelvis and abdomen was followed by a scan of the thorax, by which time (approximately 60 minutes after the end of the infusion) a positive pulmonary scan was obtained.

CASE 2

W.S., a 63-year-old white man with visible and palpable enlargement of right femoral and inguinal lymph nodes and secondary lymphedema of the right lower limb, had undergone inguinal node biopsy before referral to the Cancer Clinic and a histological diagnosis of lymphosarcoma had been made. The skin over the main node mass in the femoral triangle was shiny and purplish, and slight superficial skin ulceration was present in the inguinal crease. Bilateral lymphography was indicated for diagnostic assessment of the opposite groin and the iliac and para-aortic areas. Lymphography was done with 6.0 c.c. of ordinary LUF on the left side, and on the right side with 2.0 c.c. of plain oil followed by 4.0 c.c. of radioactive oil after demonstration of satisfactory placement of the needle. A radiograph (Fig. 2) showed filling to the para-aortic level on the left side but on the right side there was marked lymphatic obstruction at the level of the femoral nodes, and only minimal traces of opaque medium were seen in the right

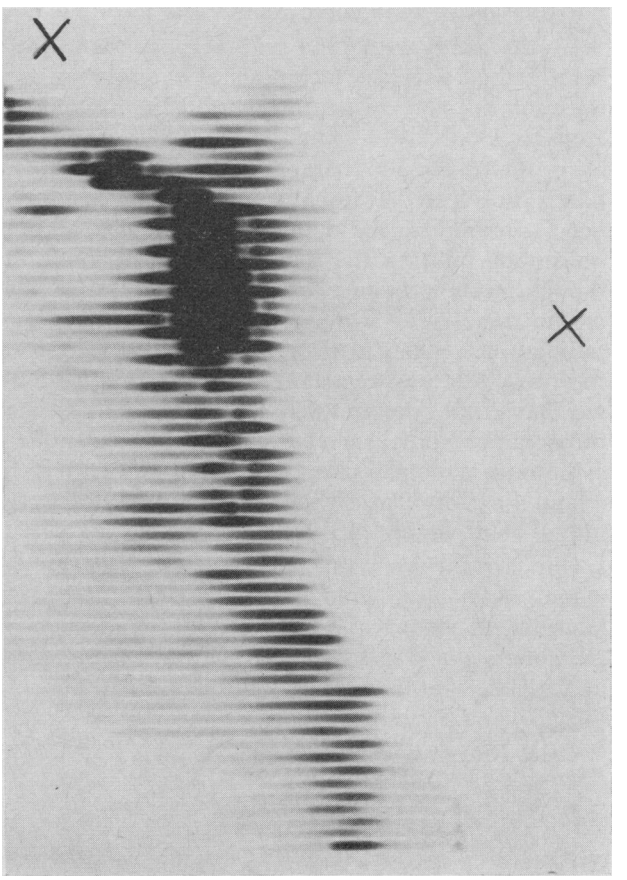

Fig. 3.—Case W.S. Photoscan of right thigh and groin. No radioactive material demonstrated above the lower iliac region. X . . . X—level of inguinal ligament.

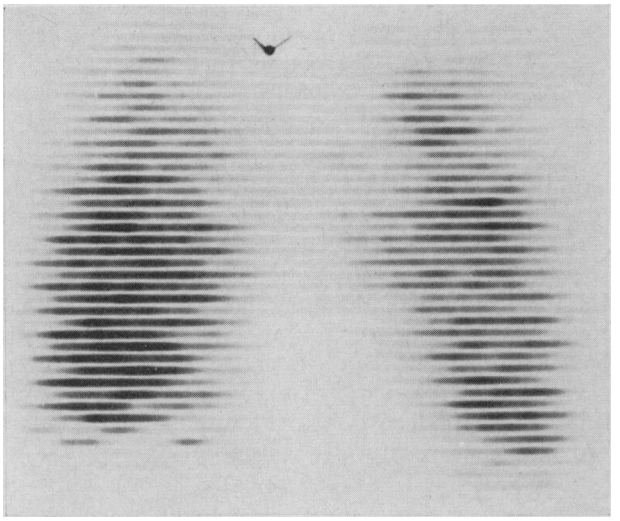

Fig. 4.—Case W.S. Pulmonary photoscan obtained within two hours of completion of intralymphatic LUF-I^{131} injection.

iliac nodes. There was no apparent upward progression to the para-aortic level on the right side. No attempt was made to overcome the obstruction by further injection of oil. On completion of the procedure the patient was placed under the Magnascanner. Radioactive material was demonstrated in the right thigh and groin and minimally in the iliac region but not in the para-aortic area (Fig. 3), confirming the radiographic evidence that the oil had not progressed proximally by the usual intralymphatic route on this side. Nevertheless a positive pulmonary photoscan was obtained less than two hours after the end of the injection (Fig. 4). Oil may have had access to the lungs via the thoracic duct on the unobstructed left side, but radioactive material was injected on the right side only. This case provides indirect evidence that lymphovenous communication had occurred by some route other than the thoracic duct.

CASE 3

R.P., a 54-year-old white woman, developed right axillary node metastasis after radical mastectomy on the opposite side for carcinoma; later a malignant pleural effusion had been controlled by intrapleural nitrogen mustard. Intralymphatic irradiation therapy to the right axilla was given on an experimental basis with the full knowledge and co-operation of the patient. Lymphatic cannulation was done on the dorsum of the right hand and infusion of LUF was begun. Preliminary radiographs of the limb showed satisfactory intralymphatic injection. A slight leakage of oil at the injection site, while insufficient to compromise a diagnostic study, prevented the use of radioactive material. Another lymphatic vessel was cannulated at the antecubital fossa. By that time the patient had already received 2.5 c.c. of plain LUF. After only approximately 1.25 c.c. of radioactive LUF had been injected at the upper site, the readings of radioactivity over the lungs began to rise and the infusion was stopped. We were especially anxious to limit total oil dosage in this patient because of the special danger of clinically significant pulmonary oil embolism in patients with pre-existing pulmonary disease. Despite the relatively small amount of total oil injected in this case subsequent lung scans were positive.

CASE 4

M.P., a 50-year-old white woman, had had a melanoma of the posterior aspect of the lower third of the right upper arm which had been treated by wide local excision and grafting, followed by discontinuous axillary node dissection, without disturbance of the pectoral muscles. Seventeen months later she developed a solitary subcutaneous mass in the medial aspect of the middle third of the arm. Investigation revealed no other evidence of disease. The new mass in the right arm appeared to be a solitary regional metastasis which was assumed to have arisen from a tumour embolus in a lymphatic blocked by the proximal axillary dissection. A lymphogram was performed by cannulating a lymphatic on the dorsum of the right hand. After injection of 0.5 c.c. of plain LUF followed by check films, 2.5 c.c. of LUF-I^{131} was injected. The procedure was monitored by shielded Geiger counters over the axilla and the opposite side of the thorax. The hand-axilla circulation time was less than one minute and the hand-lung circulation time approximately one minute. Diagnostic radiographs demonstrated small lymph nodes at the level of the first rib, which appeared to be residual nodes at the apex of the axilla but were not abnormal in size or architecture. No contrast medium was seen in or near the metastatic mass in the arm, and no radioactive uptake was detected in it. A positive pulmonary scan was obtained.

In the four cases described the specific activity of the radioactive LUF used varied between 3.6 and 4.2 mc./c.c.

In Cases 2, 3 and 4, distal stasis of contrast material in lymphatic vessels was evident on radiographs at 24 hours. Only one patient (Case 2) had clinical signs of lymphatic obstruction.

In all patients the volume of oily material injected was within the limits recommended in the literature.[11, 13, 19] In Case 1 (second treatment) monitoring of the upward progression of radioactive material by suitable probes, and cessation of injection when radioactivity was detected in the upper abdomen, did not prevent eventual arrival of radioactive oil in the lung, although this was not evident immediately upon cessation of the injection.

SPUTUM STUDIES

Induced sputum specimens are now being collected whenever possible in our patients who undergo lymphography.

Radioactivity was present in the sputa from Cases 1 (second treatment) and 3. The radioactivity 24 hours after the injection was of the order of 0.01% of the given dose, per c.c. of sputum.

Microscopic examination of sputum has been undertaken on seven suitably stained specimens from six patients, including one of the patients (Case 1, second treatment) who had received radioactive oil. Free fat was demonstrated in all

specimens. In one instance this was identified as Lipiodol by the staining technique of Felton which has previously been reported to identify LUF in pulmonary tissue sections.[20] Fatty material was demonstrably present in macrophages in three of the sputum specimens.

DISCUSSION

In reported clinical series from both sides of the Atlantic, the radiographic incidence of oil embolism has varied from 17% to 55%.[4, 5, 13, 20] Discrepancies in the incidence of radiographic detection of oily contrast medium in the lungs following lymphography have been noted, depending on the radiographic technique used.[4] The importance of lymphatic obstruction as a factor in the etiology of oil embolism during lymphography has been stressed, and the suggestion has been made that rapid shunting via distal lymphovenous communications in these circumstances is of special significance in producing radiographically detectable or symptomatic pulmonary oil deposition.[13] Clinically apparent pulmonary embolism with significant symptoms has occurred relatively infrequently,[4-6, 13, 19] but the danger is increased in patients with preexisting pulmonary disease.[13, 19] It has been suggested, on the basis of clinical and radiographic assessment, that oil embolism could be avoided by limiting the volume of oil and by radiographic monitoring of the injection.[3, 6, 11] Other studies and our own experiences indicate that pulmonary oil deposition cannot be prevented in this way and suggest that in clinical use some contrast material probably finds its way into the pulmonary circulation in all cases.[5, 12, 19, 21] Pulmonary function has been investigated after lymphography, and in a study in which oil dosage was limited to 6 to 10 c.c. in each lower extremity in adults the diffusion capacity for carbon monoxide was found to be reduced in 19 of 20 patients. The findings were correlated with histological examination of lung biopsies from five of the patients within 24 hours of lymphography.[19] The presence of radioactive material has been reported[19] in sputum collected after lymphography with LUF tagged with I^{131}. Body distribution of LUF-I^{131} has been investigated in dogs.[21] At three days an average of only 25% of the dose was retained within the lymph nodes and 50% was recovered from the lungs, although the quantities injected in the lower limb were limited to those amounts which had previously been determined fluoroscopically to fill the lymphatics up to the thoracic duct. Oil spilled into the venous circulation is apparently trapped within the pulmonary capillary bed.[5, 19, 20] In unusual circumstances or where the venous escape is massive, dangerous overflow of oil beyond the lungs evidently can occur.[22] Of occasional significance in this regard may be the existence in some subjects of pulmonary arteriovenous communications or precapillary shunts.[23, 24] Death from oil embolism to the brain has recently been reported in a patient in whom large doses of intralymphatic oil were given bilaterally into the lower limbs in the presence of lymphatic obstruction. In this case positive identification of oily contrast medium in the lung was obtained by microradiographic techniques.[22]

Until now, photoscanning of lungs after lymphography has received very little mention in the literature. In one report photoscanning one month after injection of intralymphatic LUF-I^{131} in dogs showed significant radioactivity in the nodes only.[11] Radioactivity from the lung fields has been noted under the Magnascanner in a clinical study of intralymphatic radiotherapy to retroperitoneal nodes, but it was concluded that this was not a significant hazard because postmortem examination of lungs did not show measurable activity.[12]

The biological half-life of LUF in the lungs is much shorter than that in lymph nodes,[21] pulmonary oil deposition being cleared relatively rapidly,[19] although in autopsy lung sections LUF has been identified up to 30 days after lymphography.[20] Lung radioactivity was followed for several weeks in three of the cases described here. It fell to negligible levels within seven weeks in each case.

So far only one of our patients has come to autopsy following lymphography (a bilateral lower limb study with non-radioactive oil) and no evidence of pulmonary lipid deposition was found seven months after the injection.

In this communication we have been concerned with the pulmonary deposition of intralymphatically injected material. In the cases reported here pulmonary oil deposition occurred despite limitation of the volume of oil injected in all cases, and despite monitoring over the origin of the thoracic duct for ascending radioactivity in Case 1 (second treatment). Photoscanning and sputum examination as described have been found to be sensitive means of detecting lung deposition of the injected material. Changes in the lungs may result from the presence of the oil *per se*[20] or from radiation exposure with radioiodinated oil. It must now be accepted that not only patients who exhibit clinical signs of pulmonary embolism, or who have radiographic evidence of contrast medium in the lungs, but probably all patients undergoing the procedure are exposed to long-term hazards of reactive changes induced by the material presently employed. The presence of intrapulmonary vascular shunts in physiological and pathological states suggests the possibility of a route of systemic dissemination even when intralymphatic dosage and lung overspill have not been massive.

Tracer doses of LUF-I^{131} could be added to the contrast medium in lymphographic diagnostic studies to investigate further the true incidence of pulmonary oil embolism. Where radioactive material is used for intralymphatic therapy, we would urge greater use of lung count monitoring and pulmonary photoscanning after the procedure, to permit a fuller assessment of the hazard to the lung inherent in this procedure.

Pulmonary photoscanning and examination of sputum for radioactivity and histological evidence of lipid each provide a much more sensitive method of assessing the incidence of pulmonary oil deposition after lymphography than do chest radiographs.

Our experience suggests that significant lung radiation dosage may occur even though the biological half-life of the lung radioactivity is relatively short compared with that in the lymph nodes.[21] Further study of the lung dosimetry in these circumstances is being undertaken before expanding our own clinical use of the intralymphatic therapy with radioactive isotopes.

SUMMARY

During initial experience with intralymphatic therapy using radioiodinated Lipiodol, pulmonary photoscans showed significant pulmonary deposition of radioactive material.

Sputum examination after lymphography revealed the presence of fat which could be identified as Lipiodol by a special staining technique.

Pulmonary photoscanning and sputum examination are sensitive means of detecting pulmonary oil deposition after lymphography.

The findings in this study are discussed in relation to previous reports on the incidence, control and dangers of oil embolism in lymphography.

Further study of lung dosimetry is needed in relation to intralymphatic injection of radioactive material.

The authors wish to express their thanks to Miss S. Fedoruk, M.A., Director of Physics, Saskatchewan Cancer Commission, for help and advice in beginning clinical usage of endolymphatic isotope therapy in this clinic; Dr. M. M. Fraser for his interest and co-operation in the combined treatment of patient E.L.; Dr. C. C. Merry for organizing the clinico-pathological correlation of material from that patient and for the preparation of photographs; and Miss G. Bregg, R.N., and Mr. L. Cowles for their invaluable technical help in the clinical and laboratory aspects, respectively, of this work.

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PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

URN BURIAL AND THE RESURRECTION

The mode of burial of the dead in Scotland in prehistoric times offers a wide field of interest to the ethnologist. We hear occasionally of these burial chambers, or stone cists as they are popularly termed, being opened up by the plough share, and exposed to the modern gaze. They are usually quite near the surface and are lined with rough stone slabs. The skeleton is found as a rule in a cramped or doubled up position with the limbs strongly flexed and the head bent forward on the chest. The remains are usually accompanied by jars containing food and a few weapons intended no doubt for the use of the deceased during the transit to the after life. This characteristic attitude of the body is usually supposed to be due to the exigencies of space. I always felt, however, that there was a deeper significance underlying this and on investigating the subject further found that in ancient Egypt during the prehistoric or predynastic period the usual way of disposing of the dead was to put them in this doubled up attitude in small chambers roughly lined with stones. I may mention that there is a splendid example of such a prehistoric burial in the ancient Egyptian galleries of the British Museum. A few more inquiries on this subject brought to light the interesting information that the ancient Incas of Peru were accustomed to dispose of their dead by inserting them in this characteristic attitude in huge earthenware jars which were left in the open exposed to a blazing sun until the contents become absolutely mummified. There is a fine specimen of this method of burial in the Manchester University Museum. The main outcome of these investigations was that the attitude of the remains in all the cases mentioned was found to be exactly similar to the position of the unborn child or fœtus in the womb and the result to be deduced from all these facts was that the deceased was put into the fœtal position in order to be ready for the re-birth or in other words the Resurrection. There would thus appear to be very strong grounds for believing that many primitive races were firmly convinced of the existence of an after life. It must be remembered that the stone cist burials in Scotland are supposed to belong to the pre-Christian age; for after the advent of Christianity the method of burial in the extended posture in stone coffins appears to have been almost universally adopted. The word sarcophagus is derived from the Greek words meaning "flesh" and "to eat", the idea no doubt being that the soul was alone regarded as immortal and the flesh was therefore allowed to perish. It is a very striking fact that in ancient Egypt during the dynastic and Ptolemaic periods the fœtal position was likewise given up in favour of the extended posture, and for the same explanation, namely, that the ancient Egyptian of the dynastic period thoroughly believed that the deceased possessed a double or *Ka*. This ethereal personage was supposed to leave or return to the mummy at will. In an elaborate burial of the twelfth dynasty which I had the honour to investigate eight years ago doors were painted at intervals around the coffin for the passage of the *Ka* (in some cases these doors are actually made to open). Two model boats were provided in order that the *Ka* might enjoy an occasional outing on the Nile, whilst jars containing food and several other articles of tomb furniture were likewise provided. In this relationship it is of interest to note that the almost universal method of burial with feet to the east undoubtedly originated in ancient Egypt. The River Nile runs due north and it is remarkable to note that all the tombs are situated on the western bank. The orientation of the deceased was therefore no doubt arranged with the idea that he would be in a position to face unflinchingly the dawn of the resurrection.—J. Cameron, *Canad. Med. Ass. J.*, 6: 410, 1916.