

***Papers and Originals*****LYMPHANGIOGRAPHY: NEW TECHNIQUES AND USES**

BY

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[WITH SPECIAL PLATE]

There has been a rapid growth in the application and much improvement in the methods of lymphangiography since its introduction to clinical medicine some ten years ago. This has resulted in several hundreds of reports and papers being scattered throughout many journals and written in many languages. Bibliographies have been compiled in monographs such as those of Colin (1961) and Tjernberg (1962). It is not intended to review or repeat them here, but to describe some of the advances in technique and applications that we have used in our practice.

Some explanation of the principles and terminology is necessary. Lymph vessels, for such obvious reasons as their small size, colourless contents, and the bleeding that may obscure them during surgical operations, are not readily seen. They may be visualized by subcutaneous injection of a suitable dye which enters the lymph trunks and makes them visible to the naked eye. This is termed "visual lymphangiography." We have used the dye patent blue violet for this purpose. It was first used at the Rockefeller Institute (Hudack and McMaster, 1933) for physiological studies of the minute lymphatics of the human skin. Its use in larger quantities was adapted to show the lymph trunks and nodes in clinical practice some years later (Kinmonth, 1951). Another method of studying the lymphatic system is by means of radiological lymphangiography. Here a suitable lymph trunk is first brought into view with the aid of patent blue violet and then injected with radio-opaque contrast medium so that the radiographs of the lymphatic system can be obtained in the same way as may be done with arteries or veins in arteriography or phlebography.

Information may be obtained about lymph nodes as well as vessels if sufficient dye is used. Some authors use the term "lymphadenography" when nodes are being particularly studied, and "lymphangiography" if interest is chiefly centred on the vessels. The term "lymphography" is used, particularly by Continental workers, to describe visualization of any component of the lymph pathways.

**Materials and Techniques**

Clinical techniques of identification and cannulation of lymphatic vessels have been fully described in several publications (Kinmonth, 1952; Kinmonth and Taylor, 1954; Kinmonth, Rob and Simeone, 1962). Recently certain modifications and improvements have been adopted. The investigation may be performed under local or light general anaesthesia. The injection time

for lymphography of the leg and trunk may be as long as 90 minutes when oily contrast media are used. For this reason, and also because we place the patient in a head-down position to assist haemostasis in the foot, we prefer general anaesthesia.

The patient is placed on a cassette tunnel which permits radiographs to be made of the whole body, and control films are taken. The dissection and injection of the lymphatic is facilitated by the use of an operation microscope. We use the Zeiss operation microscope with a magnification of 6 and find this especially valuable when dealing with hypoplastic lymphatics.

The water-soluble media used previously have been readily injected manually in a short period. Oily media are slower and less easy to inject. Constant attention is required of the operator to avoid any lateral movement of the syringe which might displace the needle and perforate the lymphatic. Our present technique therefore involves the use of an infusion machine, usually known as the Lund injector, which was designed by Clementz and described by him and Olin in 1961. This machine is designed to accept three syringes and therefore permits simultaneous bilateral infusion of the lower limbs should this be desired. It has a ten-speed gear mechanism which allows accurate adjustment of the infusion to a rate acceptable by the lymphatic. Any back-flow of dye along the cannula can be readily appreciated when viewed with the operation microscope. Luer-Lock syringes are used, and the syringe is connected to the cannulating needle by a 3-ft. (90-cm.) length of vinyl tubing\* (Portland Plastic 1 S.H. 700; size 1.4 mm., external diameter). This tubing is the most satisfactory available, as it is soft and pliable and may be boiled or autoclaved. We now prepare the cannulae in large numbers, pack them in polyethylene bags, and sterilize them by gamma irradiation. Autoclaving tends to make the tubing more stiff, and although boiling is less liable to produce later stiffness, great care has to be taken to avoid compressing and therefore obstructing the tubing when it is hot. We have found nylon and polyethylene tubing of similar size too resilient. This resilience may result in the dislocation of the needle from the lymphatic after it has been safely introduced. At the proximal end of the tubing a size 30 (S.W.G.) needle is secured with "araldite" epoxy resin adhesive: at the distal end a size 2 S.W.G. hypodermic needle is similarly bonded. Prior to cannulation the tubing is connected to the syringe, filled with the contrast medium, and tested for leaks.

\*Portland Plastics, Hythe, Kent.

### Visualization and Cannulation of the Lymphatic

We continue to use the diffusible dye patent blue violet† to display the lymphatics prior to dissection. It enters the lymphatics faster and is more rapidly excreted from the body than other dyes that we have tried. It has given rise to no toxic effects in 14 years of use. Recently a more purified preparation of patent blue has been produced and estimations which Professor L. Young has kindly made for us in the Biochemistry Department of St. Thomas's Hospital Medical School have shown that in a 10% aqueous solution this dye is isotonic with body fluid. After the injection of 0.2 ml. of the dye into each web space the foot is massaged and the ankle passively exercised. The lymphatic is exposed through a small transverse incision on the dorsum of the foot. If the lymphatic be obstructed about 1 cm. proximally by an assistant placing his finger on the skin, further massage will distend the vessel and cannulation will be facilitated. In a patient with thick fat forefeet the additional injection of 0.5 ml. of normal saline into each web will usually distend the lymphatic satisfactorily. If, when the needle is in position in the lymphatic, injection is commenced the vessel will dilate and small movements of the tip of the needle will be less likely to perforate the vessel wall.

With soft pliable tubing the needle usually will remain safely *in situ* when it is released. Should it appear unstable the tubing can be fixed to the skin either by a Michel clip or by tying it with a pre-inserted skin stitch. Alternatively, before cannulation is performed the needle and proximal tubing may be passed through a small stab incision in the distal skin flap.

These details are described because it is such apparently minor points which make the difference between success and failure of cannulation. The rate of injection of the oily contrast medium is approximately 1 ml. every 8 to 10 minutes. Faster rates may lead to back-flow along the needle, or to extravasation of the medium through the vessel wall which is noticed only when radiographs are taken. The usual dosage for the leg in an adult is 8–10 ml. With bilateral examinations a total of 15 ml. provides adequate filling of inguinal, iliac, and para-aortic glands. If, however, the investigation is being performed with a view to demonstrating enlarged retroperitoneal glands a larger amount of medium may be required. In the arm 3–4 ml. is sufficient to display the axillary glands. In children the dosage is reduced in a ratio proportionate to their weight (approximately 0.25 ml./kg. body weight).

Radiographs are taken at the end of the infusion while the patient is still in the operating-theatre. The lymphatic channels will be well seen, and filling of the regional lymphatic glands will be evident. Further antero-posterior and lateral films 24 and 48 hours after infusion will give additional information about the state of the retroperitoneal nodes. We find the lateral films particularly valuable (Special Plate, Fig. 1).

### Use of Oil Contrast Media

Advances in lymphography have resulted from the use of fat-soluble radio-opaque media (Wallace *et al.*, 1961). These are very useful if nodes or pathways at a distance from the site of injection are to be studied.

†Obtainable from G. T. Gurr Ltd., 136 New Kings Road, London S.W.6.

We use "ultrafluid lipiodol" (Bengué), an ethyl ester of poppy-seed oil containing 38% iodine: other similar preparations are "neo-hydriol" and "ethiodol." Such media permit excellent visualization of the lymphatic channels for up to an hour after injection. The medium may clear from the lymphatic vessel after this time, but it remains in the nodes for many weeks. The possibility that this prolonged retention of medium might produce a chronic inflammatory reaction with subsequent sclerosis and obstruction of the vessels has been considered. There has been no clinical evidence to suggest that this occurs, and experimental work we have carried out in the rabbit (to be published) to investigate this possibility has not demonstrated any harmful effect.

That the medium enters the circulation via the thoracic duct and is trapped in the lungs can be demonstrated by radiological examination. It has been our custom during our trials with oily contrast media to take chest radiographs every other day following lymphography; medium can be identified in a fine reticular pattern for up to one week. With the doses we have used the medium has produced no ill effects apart from a mild and temporary pyrexia in several instances. However, one fatality has been reported by other workers after lymphography. This occurred in a 30-kg. child who had been infused with 25 ml. of ultrafluid lipiodol and died of pulmonary oedema on the fourth post-operative day.

In our experimental work in the rabbit we have found that a dosage of oily medium greater than 1 ml./kg. is very likely to prove fatal, owing to fat embolization of the pulmonary arteries. Our dosage schedule in clinical practice has been stated above (0.25–0.3 ml./kg.), and this should be exceeded only when there is known lymphadenopathy, for in these circumstances the excess medium is taken up by the glands and does not suddenly reach the general circulation.

In the investigation of axillary or cervical lymphatics patent-blue injections should be made in the finger-webs and palm and scalp respectively. The dye-filled vessels are easily seen and cannulated in the arm, but dissection in the neck is rendered difficult by problems of haemostasis. Any infiltration with vasoconstrictors will inevitably produce constriction of the smooth muscle in the walls of the lymphatics and render them either invisible or almost impossible to cannulate. Patient dissection, however, will reveal lymphatics at a rather deeper level than in the limbs, and we have successfully performed cannulation through a post-mastoid incision.

### Diagnostic and Therapeutic Applications

*Lymphoedema.*—Abnormalities of the lymphatic vessels and glands have been extensively studied by Kinmonth and Taylor (1954), and Kinmonth *et al.* (1957, 1962), who have described a classification of primary lymphoedema. These studies were performed with the use of water-soluble radio-opaque media which give good delineation but are rapidly cleared from the vessels and nodes. Prognosis in these patients, as well as diagnosis, is helped by lymphography (G. W. Taylor, to be published).

### Diagnosis of Obscure Oedemas

When doubt exists regarding the cause of a swollen limb, lymphography may be invaluable in differentiating lymphatic defects from swellings due to venous obstructions or other causes.

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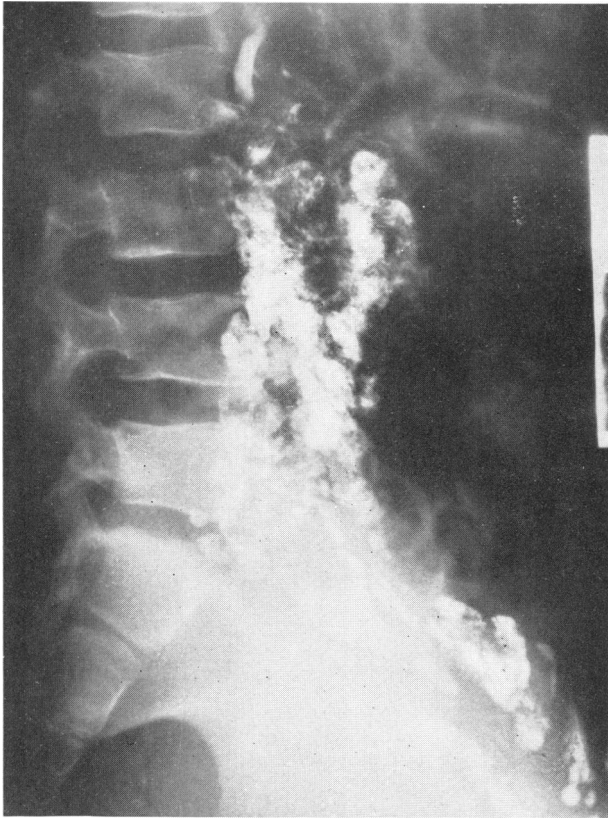


FIG. 1.—Abdominal gland enlargement in a child suffering from Hodgkin's disease.

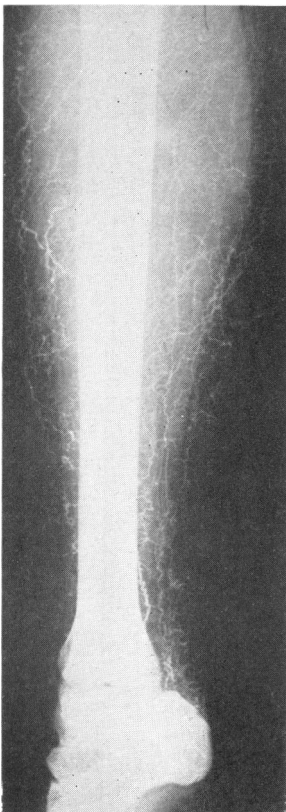
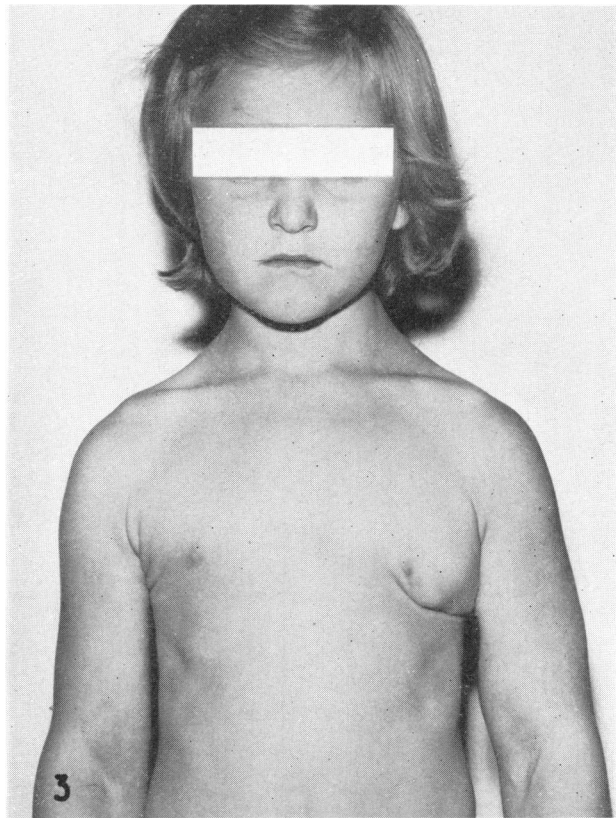


FIG. 2

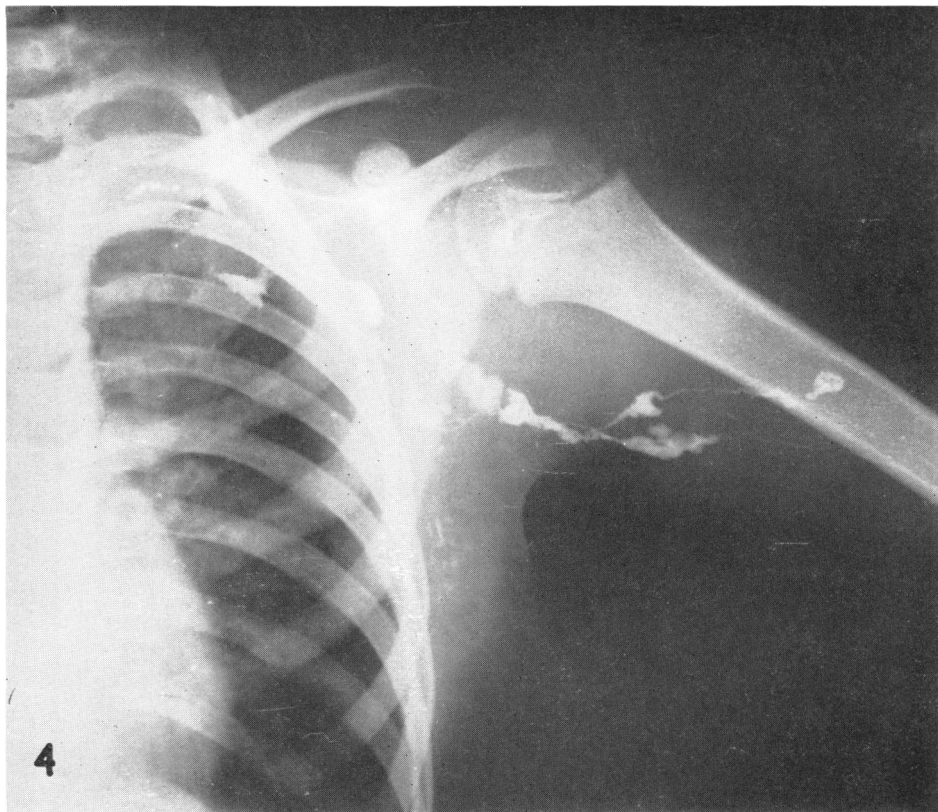


FIG. 3.—Case 2. FIG. 4.—Case 2. Upper-arm lymphogram. Medium enters large irregular lymph spaces which communicate with the swelling over lateral chest wall.

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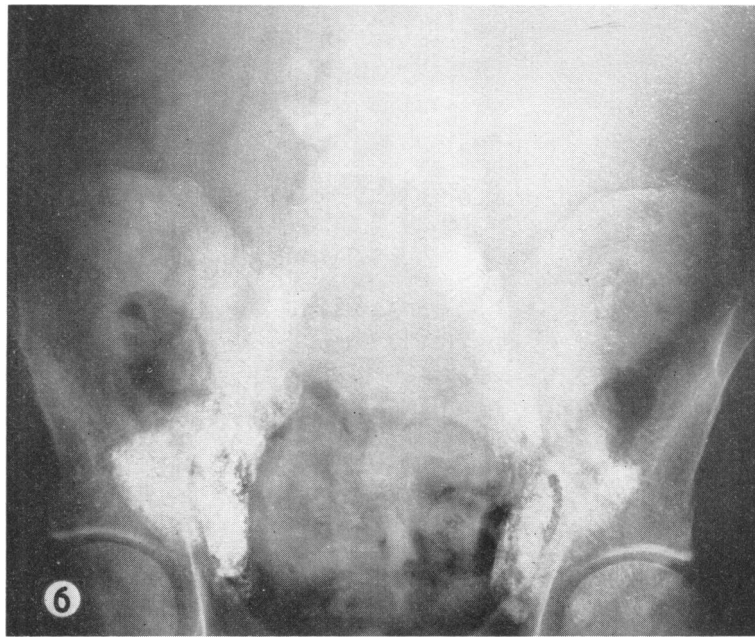
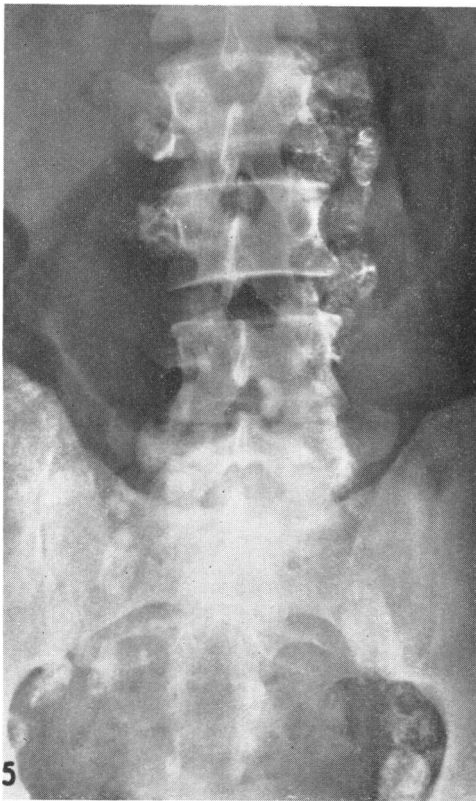


FIG. 5.—Case 3. Abdominal and iliac lymph-node enlargement due to Hodgkin's disease.

FIG. 6.—Iliac glandular enlargement in a man suffering from chronic lymphatic leukaemia.

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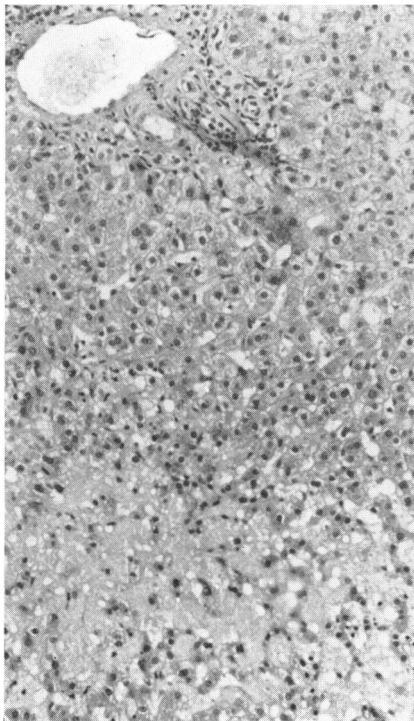


FIG. 1.—Case 1. Showing acute V.O.D. with centrolobular lagoons of blood. (H. and E.  $\times 100$ .)

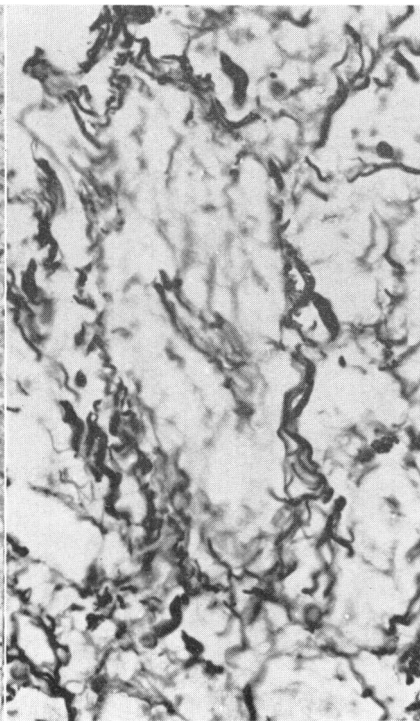


FIG. 2.—Case 1. Showing acute V.O.D. with subocclusion of centrolobular vein by subendothelial oedema of intima. (Reticulin stain.  $\times 400$ .)

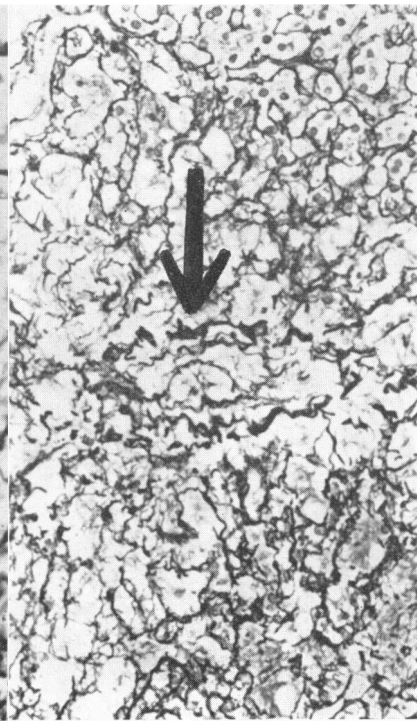


FIG. 3.—Case 2. Showing acute V.O.D. with occlusion of centrolobular vein (arrow) by connective-tissue fibres and distension of sinusoids. (Reticulin stain.  $\times 200$ .)

*Case 1.*—A 27-year-old white woman was admitted with a six-year history of swelling of the left leg. She had first noticed this after sitting for a long period during a train journey. At the time she was in the fifth month of her first and only pregnancy. The swelling persisted during the remainder of the pregnancy, and post-partum she developed some pain, tenderness, and erythema in her left groin. She was treated with anticoagulants and antibiotics consequent on a diagnosis of thrombophlebitis, and the swelling of her leg diminished but did not disappear. It had persisted, with occasional exacerbations, since that time. Clinical examination revealed an otherwise healthy woman. There were no skin changes in the limb and no dilated veins were visible. The diagnosis of primary lymphoedema as opposed to venous oedema was provided by lymphography. Ultrafluid lipiodol 11 ml. was injected into a lymphatic on the dorsum of the foot. Multiple collateral lymphatic channels were seen below the knee (Special Plate, Fig. 2): there were several lymph trunks in the thigh, but there was marked hypoplasia of the inguinal and pelvic channels and glands. A double pathological condition was excluded by the performance of intraosseous phlebograms via the medial malleolus and the greater trochanter (Schobinger, 1960).

*Case 2.*—A 6-year-old girl had been noticed to have a large left arm and shoulder since shortly after birth. Recurrent bluish swellings had occurred above the left nipple and in the left anterior axillary fold. Examination showed a diffuse swelling over the left pectoral region and left shoulder and upper arm. Her right shoulder was affected to a less extent. Above and lateral to the nipple were several nodular areas, the largest being 2 cm. in diameter. Lymphography was performed through a lymphatic antero-lateral to the tip of the medial epicondyle. Dye passed freely to the axillary lymph nodes and also into the diffuse mass and nodules. A diagnosis of diffuse lymphangioma was made. In view of the extent of the lesion surgery was considered inadvisable (Special Plate, Figs. 3 and 4).

#### Lymphomas

Recently lymphography has been used in the investigation of patients suffering from neoplastic lymphadenopathy. The investigation may have a dual function in these cases; it aids in the determination of the extent of the disease in an already diagnosed patient, and it may in some cases be used as a diagnostic tool. In either case the additional information obtained may influence treatment.

*Case 3.*—A man aged 41 had been shown by cervical-gland biopsy two years previously to be suffering from Hodgkin's disease. He had been given local radiotherapy, and his glandular enlargement had subsided. He remained well until one week prior to his second admission, when he developed evening pyrexia and recurrent epistaxis. There was no clinical or radiological evidence of glandular enlargement in the abdomen. Bilateral lymphography (8 ml. of ultrafluid lipiodol into a foot lymphatic) revealed the presence of enlarged pelvic and para-aortic glands (Special Plate, Fig. 5).

*Case 4.*—A man aged 33 had been diagnosed as having Hodgkin's disease 12 years previously following a cervical-gland biopsy. Local radiotherapy had proved successful and he had remained symptomless. Two weeks before his second admission he had experienced vague chest pains and was found to have a raised sedimentation rate. There was no clinical or radiological evidence of Hodgkin's disease. Bilateral lower-limb lymphography (10 ml. of ultrafluid lipiodol into each leg) showed para-aortic gland enlargement.

Cases 3 and 4 demonstrate the value of lymphography as a diagnostic method. In both patients recurrent Hodgkin's disease was suspected. Lymphography enabled a firm diagnosis to be made, and appropriate treatment was begun. In a third patient who was suffering from chronic lymphatic leukaemia, lympho-

graphy revealed greatly enlarged iliac glands (Special Plate, Fig. 6).

This technique has a definite place in the investigation of patients with pyrexia of unknown origin, with unexplained raised sedimentation rates, and perhaps in unexplained splenomegaly. In some instances, as has been pointed out by Wallace (1961), the enlarged glands may show a pattern of distribution of the medium which suggests the cause of the adenopathy. Our experience suggests that Hodgkin's disease may have a pattern which distinguishes it from other adenopathies, but further work is needed on lymphadenography to make differential diagnosis more precise. Tjernberg (1962) has described methods with water-soluble media that are promising.

Malignant lymphomas are treated by irradiation, chemotherapy, and steroid therapy, either singly or in combination. Factors influencing the choice of treatment are the particular lymphoma, the extent of the disease, and the presence or absence of constitutional symptoms. Patients with localized disease are usually treated by local radiotherapy. In such patients, especially if there are constitutional symptoms, a fuller knowledge of the extent of the disease may be very helpful in deciding whether steroids or chemotherapeutic drugs should be used initially. Such information may be obtained by lymphography.

*Case 5.*—A 49-year-old man attended St. Thomas's Hospital complaining of a slowly increasing swelling on the left side of his neck which had been present for the previous six weeks. There were no other symptoms. Examination showed a mass 7 by 7 cm. in the left posterior triangle, fixed to deep structures but unattached to skin. Two other small glands were palpable below this mass, but otherwise no abnormality was detected clinically or radiologically. Bilateral lower-limb lymphography was performed (10 ml. of ultrafluid lipiodol into each limb) and good visualization of enlarged and abnormal para-aortic glands was achieved. Cervical-gland biopsy proved he was suffering from reticulum-cell sarcoma. Treatment with local radiotherapy resulted only in the disappearance of the cervical mass. Should this man develop symptoms of constitutional disturbance abdominal irradiation will be started. The size of the abdominal glands under the influence of such therapy will be followed radiologically, as the medium remains in the glands for many weeks.

Using fat-soluble contrast medium, Fisher *et al.* (1961) demonstrated the presence of metastases in lymph nodes. Further experience is necessary before an accurate assessment can be made of the clinical value of this application of lymphography. It may prove helpful to the surgeon in his decision whether to perform a block dissection of regional glands after removal of a primary tumour, in particular a limb melanoma or penile epithelioma; it will also help to determine the extent of spread of testicular neoplasms to the para-aortic glands.

#### Endolymphatic Radiotherapy

With the knowledge that infused medium is distributed throughout the draining lymph nodes new possibilities for therapy become apparent. Jantet (1958, 1962) working in this department, investigated the properties of colloidal radioactive gold and determined the size of particles which would be retained in the regional nodes. After excision of the primary lesion we now infuse  $^{198}\text{Au}$  into the appropriate lymph trunks (and thence into the regional nodes) of all patients suffering from malignant melanoma of the limb. This is done

in the absence of clinical adenopathy: it is in these patients that endolymphatic radiotherapy may be most effective in destroying early malignant emboli in the sinuses of the node. Iodine has a longer half-life than gold and may prove to be a more satisfactory isotope.

With intralymphatic  $^{198}\text{Au}$ , doses for the leg have been from 50 to 70 mc., and in the arm from 30 to 40 mc. These dosages are infused in a volume of approximately 30 mc./ml. at a rate of about 0.4 ml./minute. More rapid infusion should be avoided, as any extravasation through the lymphatic will produce a high local concentration with risk of later radionecrosis. During the next few days there may be a brisk local reaction at the gland sites—for example, inguinal region—which subsides after a period of 6 to 10 days to leave the glands somewhat enlarged and indurated. The results in a small group of patients followed up for periods extending to three years have been encouraging.

There have been no published reports of the clinical use of endolymphatic cytotoxic agents in the treatment of lymphomas or secondary deposits. The possibility that these agents, some of which are rapidly hydrolysed on contact with tissues, might produce an acute inflammatory reaction and later lymphatic obstruction will have to be carefully considered.

### Summary

Clinical lymphography using water-soluble dyes was described in 1951. Following the recent development of oily contrast media which are slower and more difficult to inject, a new operative technique was required.

Oily media are retained in the lymph nodes for longer periods of time than water media. This enables a fuller study of both the channels and the nodes themselves to be made. Animal experiments and clinical trials have shown that in the recommended dosages no harmful effects arise from these new media.

Experiences with oily media are discussed in relation to the diagnosis of oedema of obscure origin and in the determination of the presence or degree of spread of lymphomas.

Lymphography may also be used to detect the presence of secondary deposits in regional glands in conditions such as epithelioma or melanoma.

The use of endolymphatic  $^{198}\text{Au}$  is described as a method of delivering high local doses of radiation to such regional glands. Preliminary results of a clinical trial are encouraging.

We are grateful to Mr. D. Ruff for technical assistance, to the Photographic Department of St. Thomas's Hospital for the illustrations; to Messrs. Bengué & Co. Ltd. for supplies of ultrafluid lipiodol, and for a grant towards our expenses; and to Mr. L. Crook, United Kingdom Atomic Research Authority, Wantage, Berks. for help in sterilizing lymphatic cannulae by gamma-radiation.

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## VENO-OCCLUSIVE DISEASE OF LIVER

BY

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[WITH SPECIAL PLATE]

Veno-occlusive disease of the liver (V.O.D.) has been recently recognized as a separate entity. The disease is seen predominantly in children, but it has also been reported in adults (Stuart and Bras, 1957). In the acute stage the small hepatic veins are involved and to a less degree the medium-sized vessels. The blockage is due to subendothelial oedema, as a result of which massive centrilobular congestion occurs which leads to a varying degree of destruction of liver cells (Jelliffe *et al.*, 1954; Bras and Hill, 1956).

Clinically, the acute stage is characterized by rapid development of abdominal discomfort, pain in the right hypochondrium, ascites, and an enlarged, tender liver. Some patients recover in four to six weeks, the results of liver-function tests and the histology becoming normal. A number, however, die in the acute stage from liver failure, while others pass into a subacute or chronic stage. The chronic phase is characterized by a picture of cirrhosis of the liver which is indistinguishable from that of other forms of cirrhosis (Stuart and Bras, 1957).

In the acute stage the diagnosis is usually based on the history, the characteristic clinical picture, and the liver-biopsy findings (Stuart and Bras, 1957).

V.O.D. has a world-wide distribution in both man and animals (Hill, 1960), and in human beings the disease occurs in Jamaica (Jelliffe *et al.*, 1954), Jerusalem, Egypt (Hashem, 1939), and Johannesburg (Higginson *et al.*, 1957). It is possible that many of the reported cases of "idiopathic" Budd-Chiari syndrome are examples of V.O.D. (Sherlock, 1958). Selzer and Parker (1951) have reported a series of cases from South Africa which began as acute Budd-Chiari syndrome and were due to eating bread made from inadequately winnowed wheat contaminated by a species of weed, *Senecio*. There is an increasing weight of evidence that a number of bush-teas taken for medicinal and other purposes in Jamaica are responsible for V.O.D. (Bras *et al.*, 1957). Tirumurti and Radhakrishna Rao (1934) hold the view that the childhood cirrhosis seen in India may be of similar aetiology, but no case of V.O.D. in adults has