Radioactive Colloidal Gold Measurements of Lymph Flow and Functional Patterns of Lymphatics and Lymph Nodes in the Extremities[1,2]

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Radioisotope techniques have been devised and standardized in this laboratory (1,2,3,4) which are useful in studying the dynamics and functional pathways of lymph flow together with lymph node pickup and filtration function. These aspects are so closely interrelated as to suggest that combined simultaneous study by one technique might result in a more complete and better integrated concept of lymph flow. Radioactive colloidal gold (AU^{198}), average particle size 3.0 millimicrons, has been found acceptable for such combined study. Using one injection, a set of observations is made which includes all four aspects. Colloidal gold (AU^{198}), 15-25 microcuries in 0.1 cc liquid,[7] is injected without operative exposure, into the particular lymphatic compartment of the extremity to be studied such as subcutaneous, skin or muscle. Because of its colloidal, metallic nature and size, it is carried in the lymph. Some colloidal gold (AU^{198}) is deposited in the first station of lymph nodes within minutes. Some is routed to second and third stations of nodes, particularly after the first station is loaded. Colloidal gold (AU^{198}) which enters a node remains there for the duration of the study, so that deposition of colloidal gold (AU^{198}) measures filtration function of the node. Lymph nodes of the extremity filter out most of the colloidal gold (AU^{198}). The remainder, however, bypasses all nodes to enter the thoracic duct and blood from which it is quickly cleared by the reticuloendothelial cells of the liver.

Because it is a gamma emitting isotope, colloidal gold (AU^{198}) can be traced and measured in its passage through the lymphatics and sites of deposition in the lymphatic system by means of external measurement techniques. Following injection, there is no operative interruption of continuity of the experiment. Be-

cause of its half life, 2.69 days, *in-vivo,* serial, continuous or interrupted quantitative observations can be performed over a period of several days, so that physiologic as well as complex disease states can be adequately studied under varied conditions. Because of the minute amount (0.1cc) used, there is no artefactual distention of lymphatics. The measurements of dynamics and pathways of lymph flow truly represent physiologic and pathologic states studied.

In the search for an ideal isotopic material for studying lymph flow, various materials labeled with radioisotope were injected into different lymphatic compartments and sites in normal volunteers (Table I). Prior to this study, unaltered $RI^{131}HSA$, had been used for quantitative study of lymph flow. The rate of disappearance of unaltered $RI^{131}HSA$ from the site of injection in an extremity has been used as a measure of lymph flow (5). Concentration in the blood and urine has also been used to measure the amount of $RI^{131}HSA$ which traversed the lymphatic system to reach the thoracic duct and thus the blood stream. However, our experiments in dogs and humans, including direct cannulation of extremity veins, indicate that these measurements with $RI^{131}HSA$ are not specific. Significant amount of I^{131} in $RI^{131}HSA$ enters the blood directly from the site of injection. Disappearance rate and blood concentration of $RI^{131}SHA$ do not indicate passage through the lymph exclusively, but include direct blood absorption. By contrast, experiments involving direct cannulation of extremity veins indicate that only a minute and insignificant amount of colloidal gold (AU^{198}) which leaves the site of injection is transported through the blood. Practically all of the colloidal gold (AU^{198}) which leaves the site of injection enters the lymphatic system.

Further transport of colloidal gold (AU^{198}) is entirely through lymphatics. Segmental measurements, described below, have been defined, which indicate the amount of colloidal gold (AU^{198}) in the lymphatics of various anatomic segments of the limb. These important measurements are not possible with unal-

TABLE I

STUDY OF CHIEF LYMPHATIC COMPARTMENTS OF EXTREMITIES WITH VARIOUS
RADIOISOTOPE MATERIALS.

Type of Cases	Isotopic Material	Injection Plane	Site	No. of Cases
1) Normal human volunteers	Radioactive colloidal gold (AU^{198})	Subcutaneous	Foot	45
2) Normal human volunteers	Radioactive colloidal gold (AU^{198})	Intramuscular	Leg	20
3) Normal human volunteers	Natural $RI^{131}HSA$	Subcutaneous	Foot	11
4) Normal human volunteers	Heat denatured $RI^{131}HSA$	Subcutaneous	Foot	4
5) Normal human volunteers	Radioactive colloidal gold (AU^{198})	Intradermal	Foot	5
6) Normal human volunteers	Radioactive colloidal gold (AU^{198})	Subcutaneous	Hand	4

LIVER

SPLEEN

DEEP ILIO—AORTIC NODES →

SUPERFICIAL
FEMORO—INGUINAL →
NODES

SEGMENT
(d)

SEGMENT
(c)

SEGMENT
(b)

SEGMENT
(a)

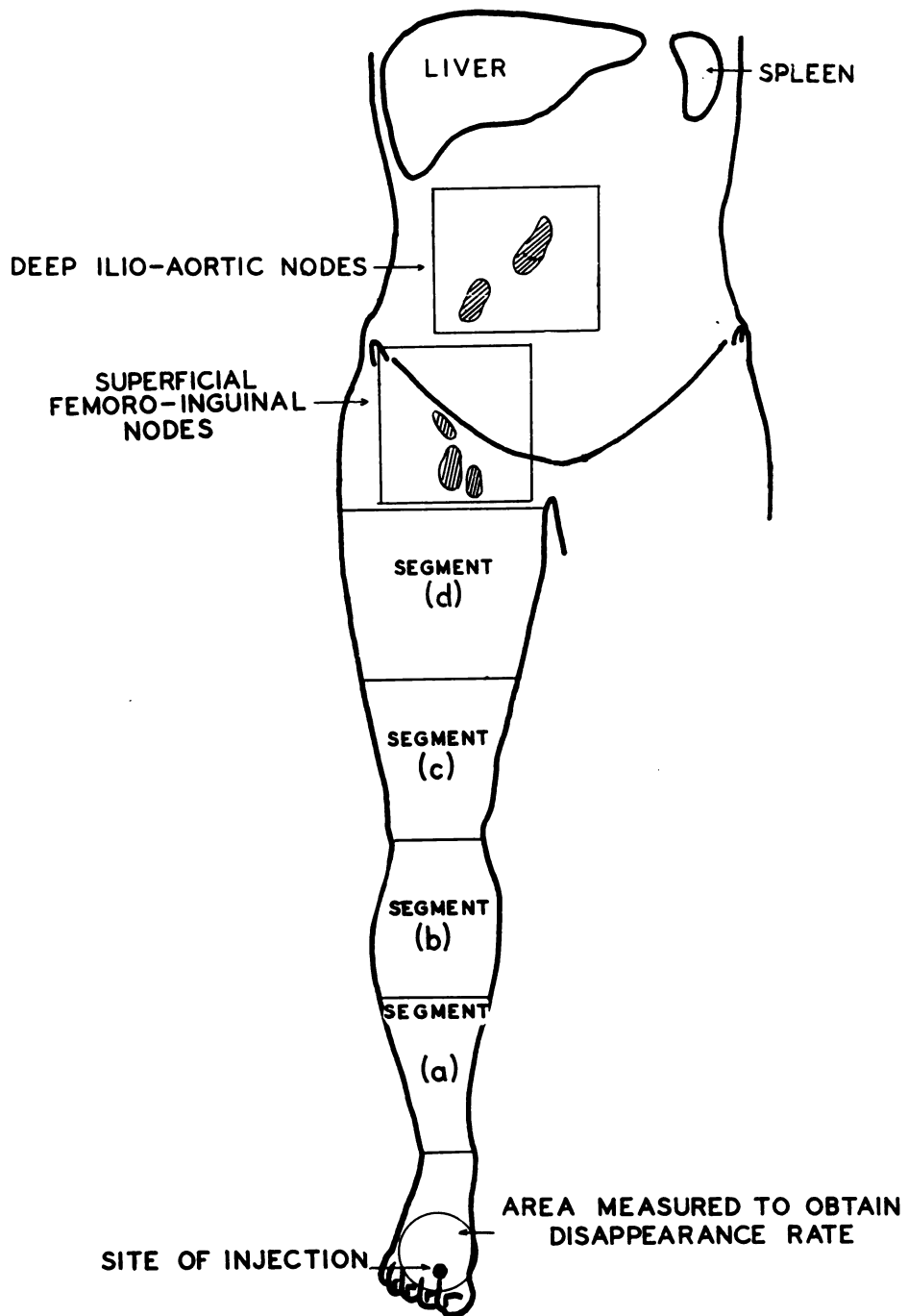AREA MEASURED TO OBTAIN
DISAPPEARANCE RATE

SITE OF INJECTION

Fig. 1. Colloidal gold (AU^{198}) measurements of lymph flow

1) Disappearance rate $= \dfrac{\text{amount disappeared}}{\text{amount injected}} \times 100\%$

Amount disappeared = amount injected − amount remaining at the site of injection

2) Distribution of colloidal gold (AU^{198}) at various points in the lymphatic system. All measurements recorded as per cent of the disappeared amount.

tered RI[131]HSA because concentration of isotope measured in each segment of the limb is very small in the early and critical phases of disappearance, and the amount which enters the blood directly from the site of injection with RI[131]HSA negates the measurement. Also, concentration of RI[131]HSA builds up continuously in the blood over a 72 hour period, due to the continued disappearance from the site of injection, and recirculates in the lymph. This makes later measurements, for example at 24 hours, of concentration of isotope in the lymph of various segments of the limb, impossible. By contrast, after about 6-12 hours, colloidal gold (AU[198]), unlike RI[131]HSA, ceases to leave the site of injection, in most patients as can be seen in the disappearance curves (Fig. 4).
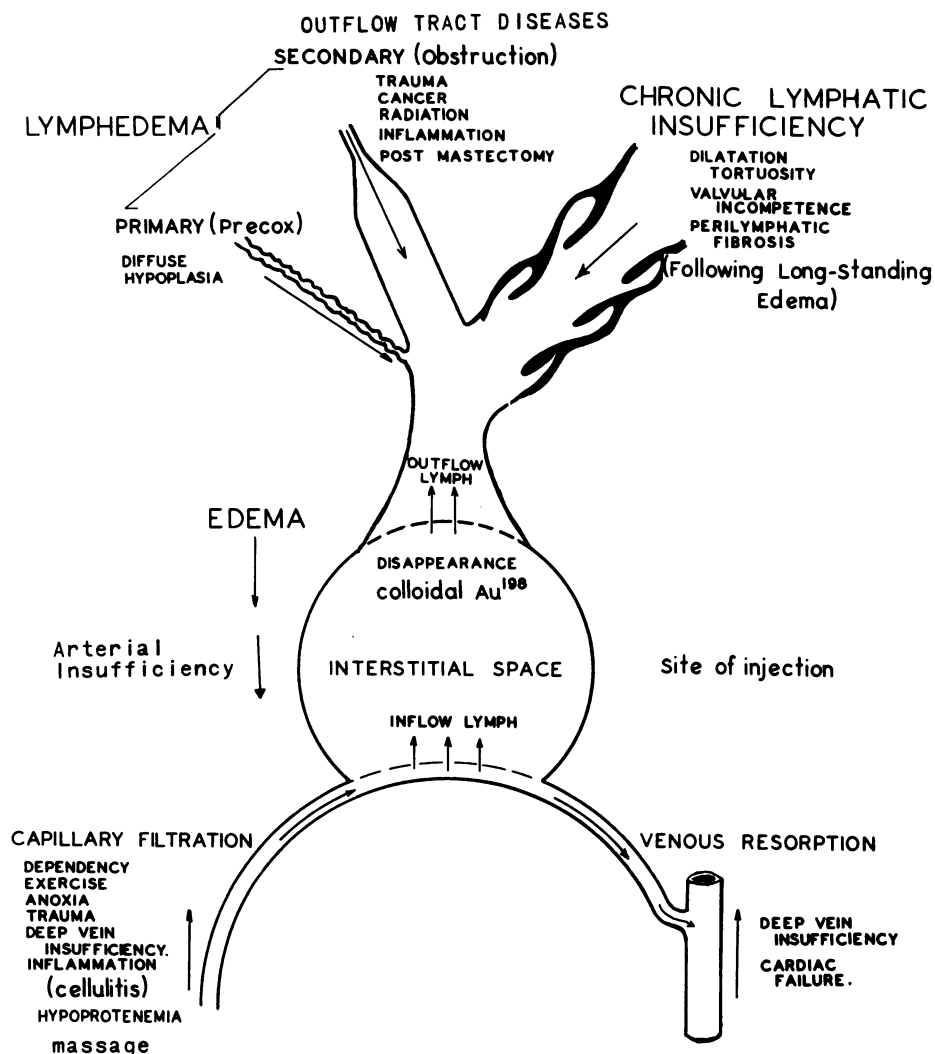

Fig. 2. Disappearance rate of colloidal gold (AU[198]) as a measure of lymph flow in normal patients and patients with edema of extremities.

After twenty four hours there is no further disappearance in any patient. Thus, any colloidal gold (AU^{198}) which is found in the segments after 24 hours indicates a "residue" in the lymphatics. The amount of total segmental-residue at 24 hours and the presence and amount of residue in individual segments is important in defining lymphatic disease states.

Unaltered RI^{131}HSA is not picked up by lymph nodes. By contrast much, but not all of the colloidal gold (AU^{198}), is picked up and filtered out by the lymph nodes in the extremities. Quantitative measurement of deposition and by-pass of various anatomic groups of lymph nodes by colloidal gold (AU^{198}) indicates functional pathways of lymph flow from different sites and tissues under varying conditions. The measurement of colloidal gold (AU^{198}) which has been deposited in nodes also defines the dynamics of lymph flow since it indicates passage through the lymphatics of the extremity. Because of by-pass of nodes, some of the colloidal gold (AU^{198}) escapes filtration. Measurement of time and amount of liver deposition of colloidal gold (AU^{198}) accurately reflects passage through the entire lymph circulation without filtration by nodes. This may be a useful parameter in defining diseases of the lymphatic system.

Method of Study of Lymphatic System

Intitial study in the lower extremity is made by injection of 0.1 cc of colloidal gold (AU^{198}) into the subcutaneous tissue space of the dorsum of the foot between the heads of the first and second metatarsals. The patient remains in supine position at rest for 1½ hour. At one and one-half hours after injection, the patient walks for ten minutes. After the two hour measurement, he goes out to

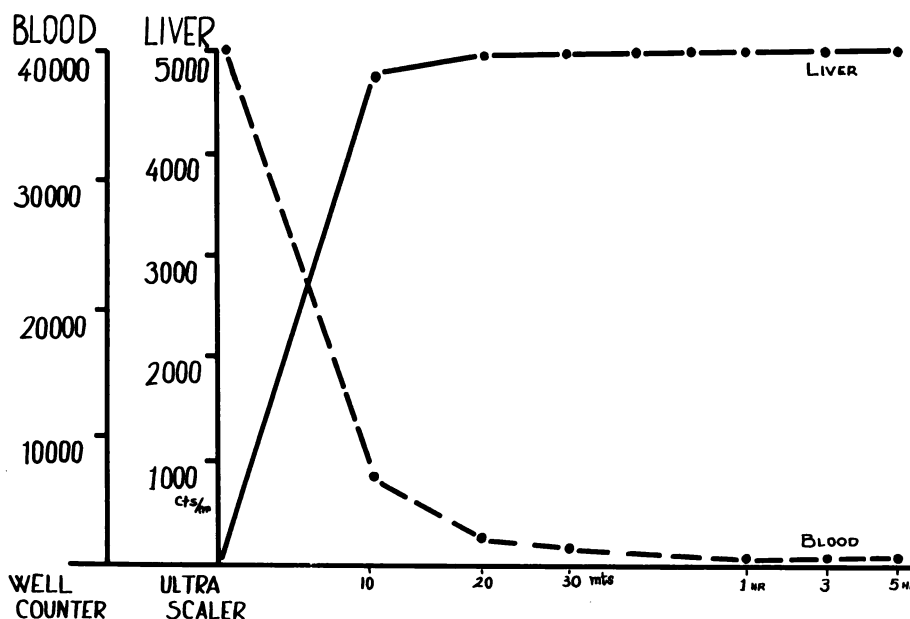Fig. 3. Pickup by liver and disappearance from blood of colloidal gold (AU^{198}) following intravenous injection—Normal Human

lunch, affording a further period of active exercise. Measurements to be described are made every 15 minutes for the first hour and then successively at two hours, four hours, six hours, 24 hours, and occasionally at 48 and 96 hours. The half life of gold permits such continuous study. Almost 100 per cent of the colloidal gold (AU^{198}) can be accounted for by external volume-counting, and traced in the lymphatic system (Fig. 1).

Subsequent studies which may be done include intramuscular injection into the gastrocnemius muscle about six inches below the knee in the midline. Intradermal injection may also be made at various levels. Study of subcutaneous, intradermal, and intramuscular lymphatic compartments using the techniques and measurements described indicate compensatory and useful lymph channels for therapy in patients with lymphatic disease.

Upper extremity study is made by injection subcutaneously into the tissue space between the first and second metacarpals. Intramuscular and intradermal injections can also be made. Exercise is performed as part of the procedure after one hour.

Measurements of Lymph Flow in Lower Extremity

Lymph flow is measured by: 1) *Disappearance rate from the site of injection.* The disappearance rate is a measurement of lymph flow at the site of injection. As shown in Fig. 2 this measurement reflects both the inflow amount of
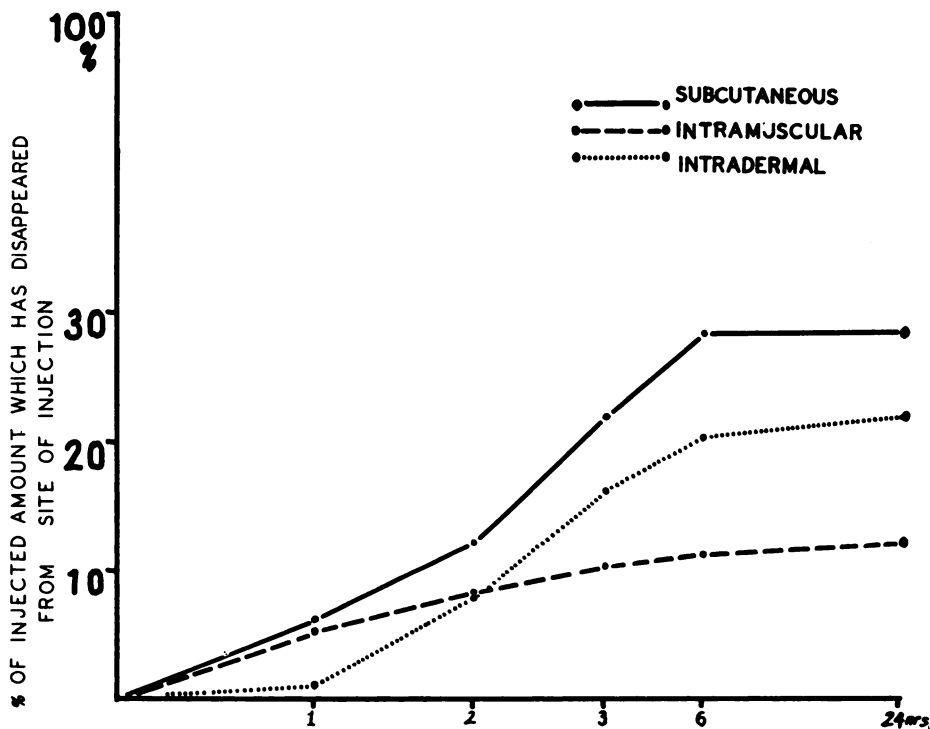

Fig. 4. Average disappearance rates of colloidal gold (AU^{198}) in chief lymph compartments of lower extremity.

lymph and the state of competency of the lymphatics. 2) *Measurements of Segments.* This and the subsequent measurements (3,4) indicate the distribution of material in the lymphatic system. The extremity has been divided arbitrarily into progressive anatomical segments from below upward, segments (o), (a), (b), (c), (d). Quantitative measurements are made of these segments which represent the progression of lymph flow from injection site through the entire extremity. Segment (o) immediately adjacent to the site of injection in the foot represents an area of direct tissue space spread of the injected colloidal gold (AU^{198}). Detailed study of the distribution of colloidal gold (AU^{198}) in segment (o), and spreading factors, will be reported separately. In the present report, segment (o) is included with the site of injection. Measurement of segments (a), (b), (c), (d), represent material transported in lymphatic channels in the extremity. Segment (a) extends from the ankle to the middle of the leg, segment (b) extends from the middle of the leg to the patella, segment (c) extends from the patella to the middle of the thigh and segment (d) from the middle of the thigh to the femoral lymph nodes. 3) *Rate and quantity of pickup in lymph nodes.* Superficial femoro-inguinal and deep ilio-aortic lymph nodes are measured separately to help define subcutaneous and deeper lymphatic flow pathways. 4) *Rate and quantity of deposition in the liver and spleen.* Using colloidal gold (AU^{198}), this represent complete by-pass of lymph nodes and entrance into the thoracic duct and blood stream. The blood is rapidly cleared of the colloidal gold (AU^{198}) which is picked up by reticuloendothelial cells of the liver (Fig. 3).
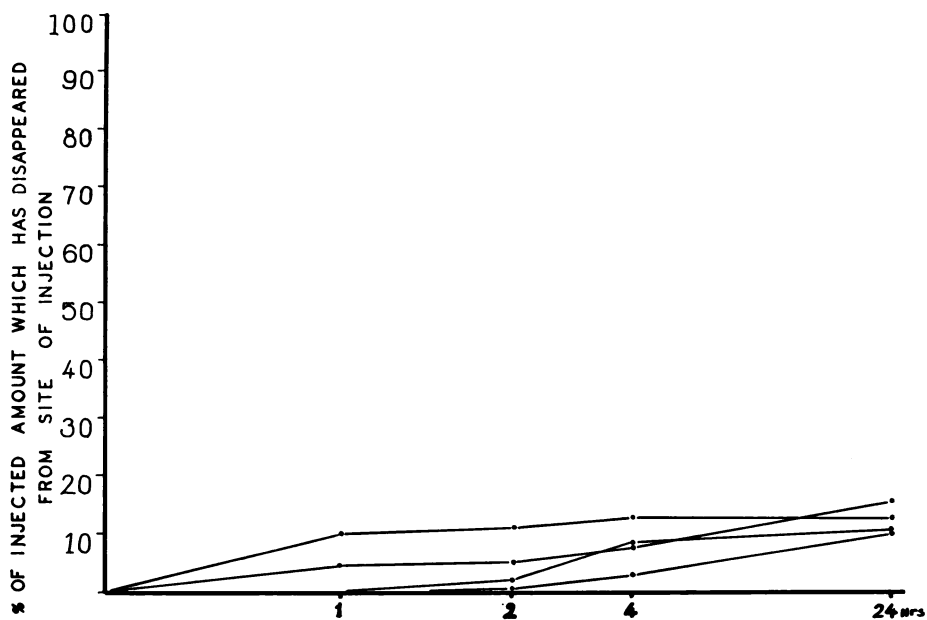

Fig. 5. Disappearance rates of colloidal gold (AU^{198}). Subcutaneous injection. Normal upper extremities. 4 patients—3″ crystal

Measurement of Lymph Flow in Upper Extremity

The upper extremity is divided into segment (a) from wrist to elbow, and segment (b) from elbow to axilla. Node pickup is measured in the epitrochlear, axillary and supraclavicular nodes. Liver and spleen measurements are the same as in lower extremity study.

Isotope Technique and Measurements

Measurements of lymph flow at the site of injection and throughout the extremity and rates and quantity of pickup in lymph nodes, liver and spleen are made by means of isotope techniques which have been standardized in this laboratory. A wooden splint was made to accommodate the foot in a suitable fixed horizontal position for measurement of disappearance rate from site of injection (Fig. 11). Lead blocks placed on a lucite platform are used to separate the various areas being measured (Fig. 11).

A 3″ crystal (Nuclear Chicago) is generally used for all measurements, although all measurements except the segments (a), (b), (c), (d), had been successfully made previously using a ¾″ crystal. Quantitative measurements of disappearance from injection site, segmental amounts, superficial and deep node and liver amounts are performed with flat field nose piece collimator system.

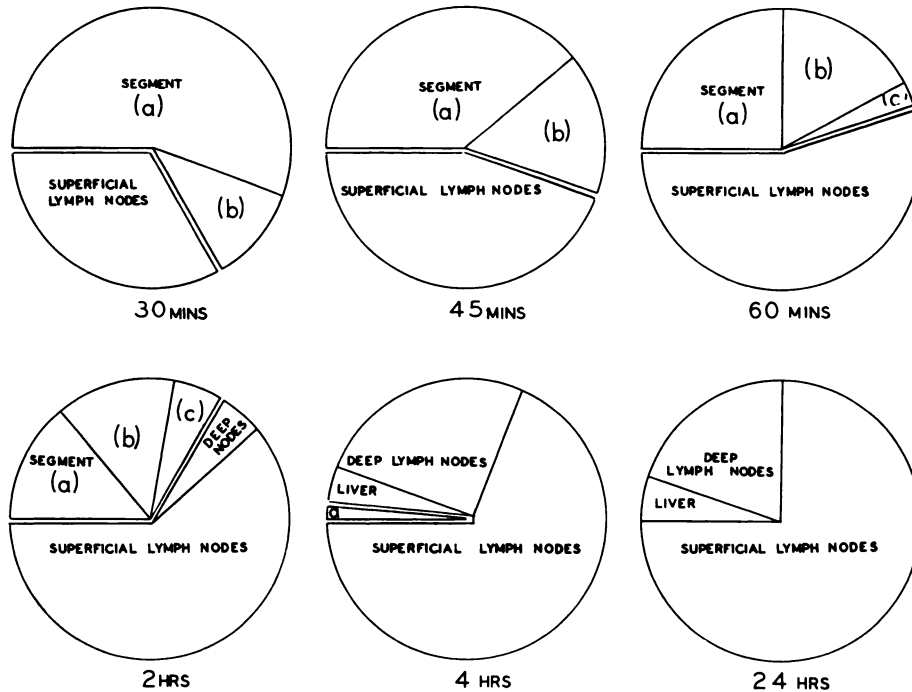All quantitative measurements are made at 30cm distance of crystal to skin,

Fig. 6. Percentage distribution of colloidal gold (AU¹⁹⁸) which has disappeared from site of injection and entered the lymphatic system Lower extremity—Normal

because of the large areas involved and large volumes being measured, particularly the segments, nodes and the liver (Fig. 9).

Injection site	10cm x 10cm x 2cm
Segment a	18cm x 7cm x 6cm
Segment b	18cm x 7cm x 6cm
Segment c	16cm x 11cm x 5cm
Segment d	16cm x 11cm x 5cm
Femoro-inguinal nodes	20cm x 20cm x 2cm
Ilio-aortic	20cm x 20cm x 2cm
Liver	19cm x 14cm x 7cm

Phantom Studies

Quantitation of small amounts of isotope in large volumes and at various depths also requires a correction factor which has been worked out by means of phantom studies for each site. No correction factor is required for measurement of the disappearance rate at the site of injection since the area is small and the source of moderate intensity and just under the skin. The concentration in segments (a), (b), (c), (d), has been simulated by homogenous distribution of small amount (2.7 microcuries) of colloidal gold AU^{198} in a volume of water equivalent to the average volume of these segments of the extremity in-vivo. Homogenous distribution was used since in-vivo colloidal AU^{198} is scattered throughout several lymphatic channels in these segments.
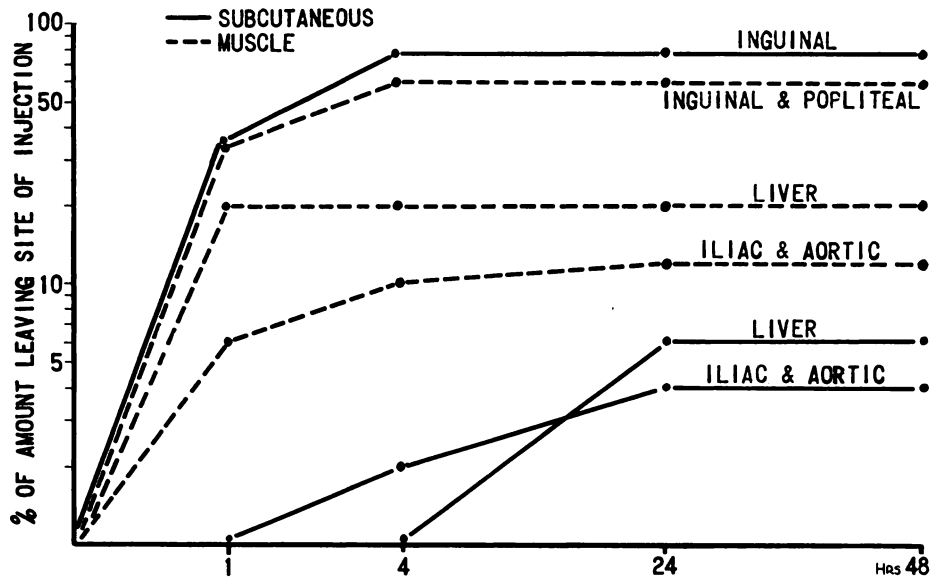

Fig. 7. Difference in node pickup and by-pass of nodes (liver) from subcutaneous (13 patients) and muscle (12 patients) compartment injection of colloidal gold (AU^{198})— Normal lower extremity
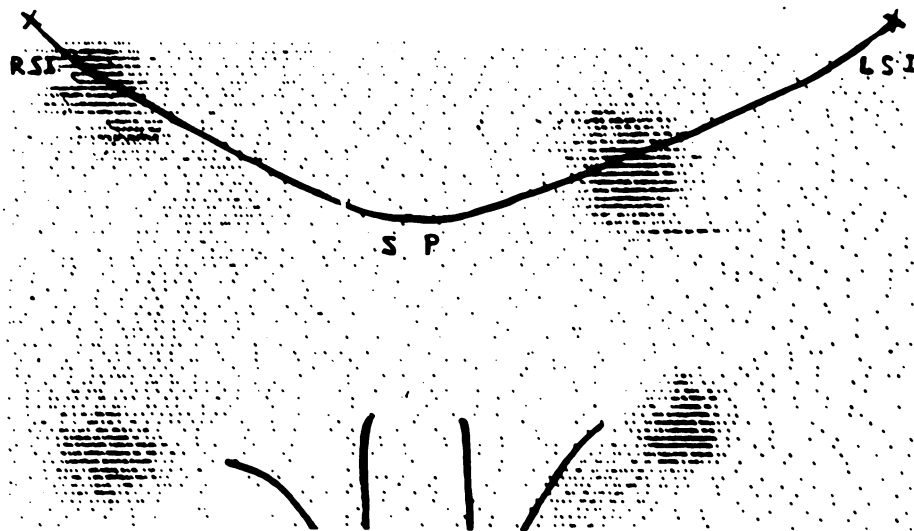
Fig. 8. Simultaneous bilateral anteroposterior scan of the groin after an injection into the dorsum of both feet. The femoral lymph nodes are generally definable in 4-6 hours and the inguinal nodes in 6-24 hours.

Concentration in the femoro-inguinal node area has been simulated by a water phantom 20cm x 20 cm x 2cm in which 10 microcuries of colloidal gold AU^{198} was homogenously distributed. The large femoral and inguinal nodes which pickup the greatest amount of colloidal gold in humans are generally 2-4
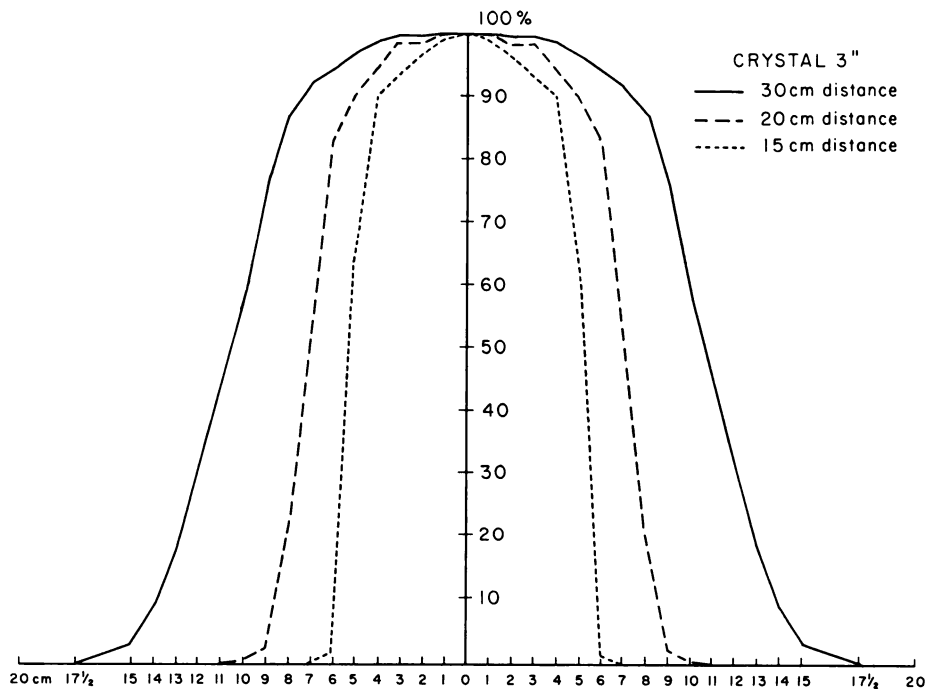

Fig. 9. Effect of distance of the crystal from the source on cts/mt measured in per cent obtained by moving a point source containing one microcurie of colloidal AU^{198} away from the central axis.

in number (Fig. 8) on each side, extending over an area averaging 12cm x 10cm. However, an almost equal amount of colloidal gold is found in the surrounding tissue containing small nodes constituting the 20cm x 20cm area.

Concentration in the ilio-aortic nodes was simulated in a bony pelvis by placement of two capsules each containing 0.16 microcuries, colloidal AU^{198}, one at the level of bifurcation of the iliac vessels and the other slightly above the sacral promontory. The bony pelvis was kept in a position simulating supine position of the body and measurement done with the crystal 30cm above the level of the inguinal ligament. The same procedure is followed in-vivo since measurement at 30cm from the inguinal ligament overcomes the problem of variation in the thickness of the abdominal wall and abdominal contents.

A water phantom reproducing the exact shape, dimensions and placement of the liver in the body and containing 2.0 microcuries, colloidal AU^{198} distributed homogenously was used for standardization of measurements of this organ.

Correction Factors

Correction factors to be added to in-vivo measurements made at 30cm from the skin have been worked out by means of such phantom studies as follows.

Segment a	12%
Segment b	12%
Segment c	20%
Segment d	20%
Femoro-inguinal nodes	22%
Ilio-aortic nodes	40%
Liver	86%

Scanning of femoral and inguinal lymph nodes have been performed using Nuclear Chicago Scintiscanner Model # 1700, window = 10, speed = 45, base level = 361 with pulse height analyzer, high voltage, 3" crystal. A 64 hole focusing collimator (Nuclear Chicago) with focal point 7cm below the collimator opening is used. 32-128 counts per dot over the femoro-inguinal node area produce a good scan in about 30 minutes. Superficial nodes in the femoral and inginal area are located about 2cm below the skin in the average patient. Confirmation of focus on lymph nodes is made by moving the collimator up and down to obtain maximum count. Scans made with ¾" crystal and a cone can discriminate between nodes at ½cm separation while those with 3" crystal can discriminate at 1cm. However, the minimum amount of colloidal AU^{198} which can be scanned increases to ½ microcuries from ¼ microcuries when ¾" crystal is used.

For measurements in segment (o), a ¾" thick lead collimator was made with 1 cm openings 1 cm apart (Fig. 12). This is used in combination with the 64 hole focusing collimator and 3" crystal. Less than 0.1 per cent of colloidal AU^{198} is found to traverse the septa, in the intensity range used. A grid with smaller openings can also be used for measurements of concentration in node groups and parts of nodes. (Fig. 10)

Recording of Measurements

Disappearance is recorded as per cent of injected amount of colloidal gold (AU^{198}) isotope. All other measurements are recorded as per cent of the amount of colloidal gold (AU^{198}) which has disappeared from the site of injection. Thus, distribution of material at various points in the lymphatic system is measured as per cent of the amount which has entered the lymphatic system.

Results: Disappearance Rate
Normal Subcutaneous—Lower Extremity

Disappearance rates in normal humans following subcutaneous injection of lower extremity range form 18-39 per cent at 24 hours, (Fig. 4). Variation is due to particle- size and site and plane of injection and local tissue factors. Although phagocystosis is a factor, studies in dogs indicate that 88-100 per cent
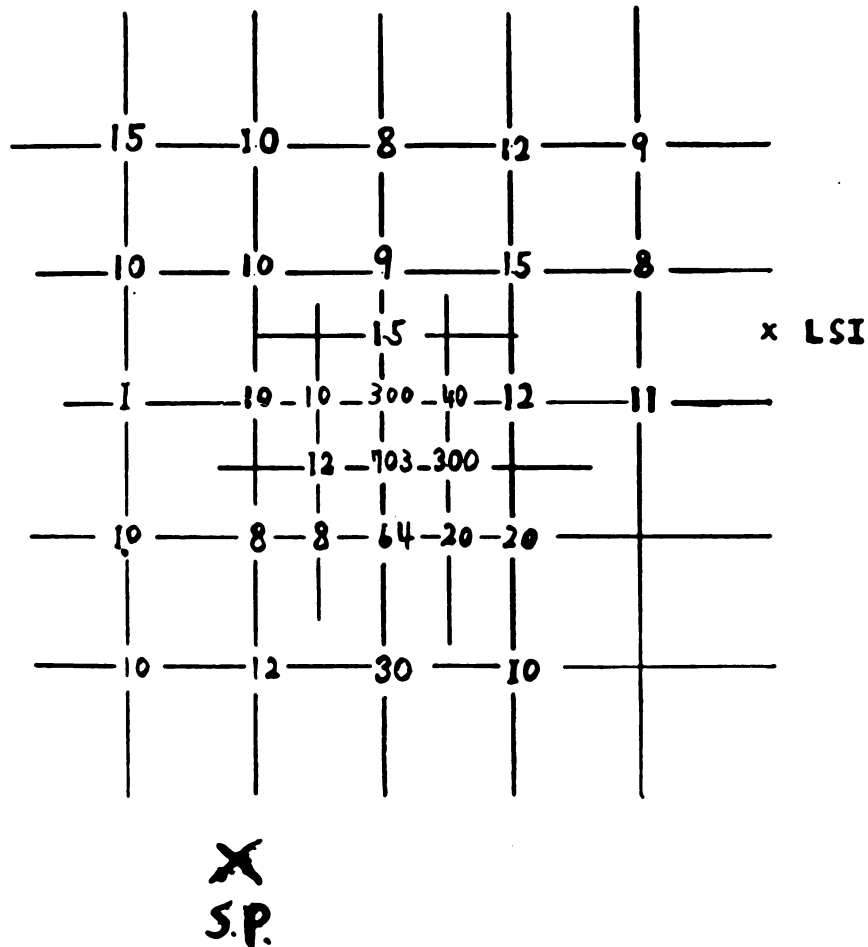

Fig. 10. Grid counting of pickup by inguinal lymph node colloidal gold AU^{198} injected into foot. Actual size

of the colloidal gold (AU^{198}) in the afferent lymphatics is found in the super-natent lymph after centrifugation. Much of the disappearance from one to four hours is the result of exercise. The rise between one and two hours, in response to the initial controlled exercise-period of ten minutes, is generally greater than the rise between two and four hours, when the patient walks to lunch. When the patient is kept at rest, without exercise, there is much less disappearance in the first four hours. Despite the wide variation in disappearance rates in normal humans (18-39 per cent), patients with abnormal extremities show abnormal disappearance rates whose significance is readily identified (Table II).

Disappearance rates from intramuscular injection of normal lower extremities are shown in Fig. 4. After about one hour, disappearance ceases. Disappearance rates from intradermal injection of normal lower extremities are shown in Fig. 4. The amount of disappearance indicates both muscles and skin to be important lymphatic compartments.

Disappearance rates from normal upper extremity subcutaneous injections are shown in Fig. 5. Disappearance is slower than from lower extremity, perhaps because of the fact that dependency and exercise result in a greater amount of lymph in the lower extremity.

Segments (a), (b), (c), (d)—Normal (Fig. 6) Subcutaneous Lower Extremity

The amount in the segments is directly related to the amount disappearing from the site of injection and the competency of the lymphatics. During the first
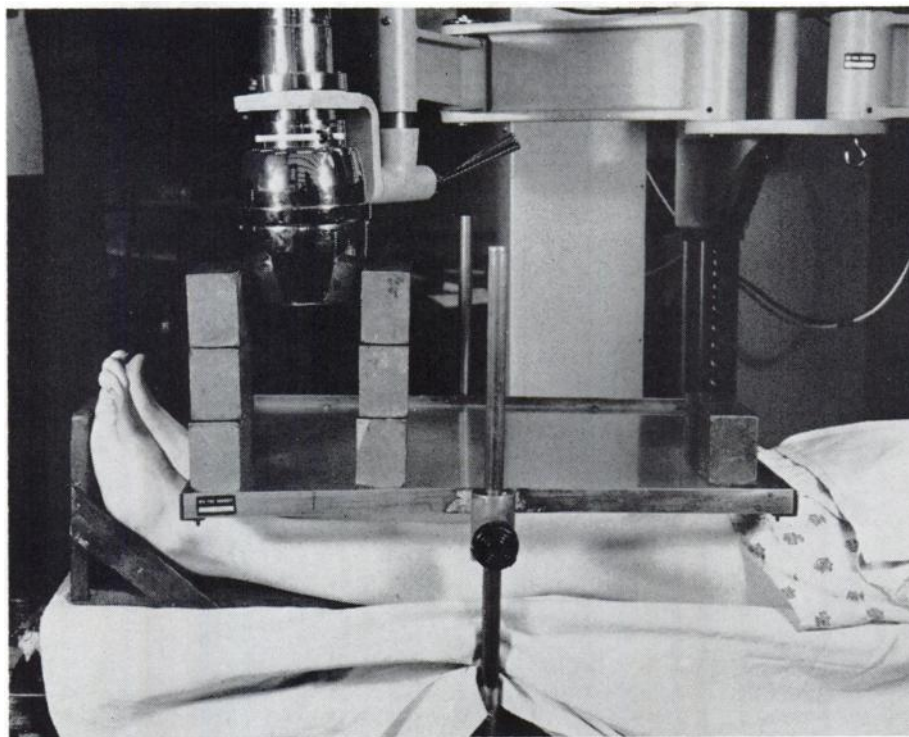

Fig. 11

TABLE II

DIFFERENTIAL DIAGNOSIS OF ABNORMAL EXTREMITIES BY MEANS OF DISAPPEAR-
ANCE RATE AT 24 HOURS (GROUPS I TO IV) AND THE PRESENCE OR ABSENCE OF
SEGMENTAL RESIDUE AT 24 HOURS (GROUPS A AND B). SUBCUTANEOUS LYM-
PHATICS STUDY USING RADIOACTIVE COLLOIDAL GOLD (AU198).

Group A	*Group B*
Segmental residue at 24 hrs.	*No segmental residue at 24 hrs.*
Group I (0 to 3%) Primary Diffuse Lymphedema (Precox) (Case 1 to 5) Severe Secondary Lymphedema Post-radical mastectomy (Case 8 to 13) Cancer (Case 6) Trauma (Case 7)	No cases in this group
Group II (3 to 17%) Moderately severe secondary lymphedema Post-radical mastectomy (Case 14 to 17)	
Deep vein insufficiency with long standing edema producing chronic lymphatic changes and severe lymphatic insufficiency (Case 18 & 19)	Deep ulcerations at ankle, chronic varicosities but no deep vein insufficiency (Case 20 to 22)
Group III (18 to 39%) Deep vein insufficiency with long standing edema and chronic lymphatic insufficiency, less severe than group II A (Case 25 to 30)	Deep vein insufficiency with edema (not as long standing as Group III A) (Case 31, 32, 34, 35, 36)
	Dermatitis ⎞ No significant (Case 40 to 42) ⎪ involvement Chronic varicose ⎬ of deep veins (Case 37 to 39) ⎪ veins or Other abnormalities ⎠ lymphatics
Group IV (40+ %) Deep vein insufficiency complicated by acute cellulitis (acute lymphatic overloading, edema of short duration). (Case 45 to 48)	Deep vein insufficiency without edema (Case 50 to 53) Acute Cellulitis (Case 54) Cardiac failure edema, short duration (Case 55)

hours, at rest, in the normal patient, segmental amounts (a) and (b) increase progressively and account for the most of that which disappears. Concentration in (a) is generally higher than in (b) although occasionally equivalent. With exercise, *i.e.* after one and one-half hours, rapid passage of all material out of (a) and (b) segments occurs. When the disappearance rate continues to rise after two hours, the amount in the segments may remain relatively high because of entrance of new material. The tracer material does not generally appear in significant amount in segment (c) until the two hour period, after exercise. The concentration remains low, indicating rapid passage through this area in the normal. Measurements at four and six hours show no material in the segments unless disappearance continues in significant amount, which is unusual. At 24 hours no material remains in the segments in the normal.

Segmental residue at 24 hours is useful in identifying etiology of edema (Table II), and the site and degree of insufficiency of lymphatics. Specific segmental residues localize the site of lymphatic disease.

Node Pickup

Node pickup and segmental amounts are inversely related, in the normal as well as abnormal (Fig. 6). Femoral, inguinal and iliac node pickup represents material which has passed through all the segments. 80 to almost 100 per cent
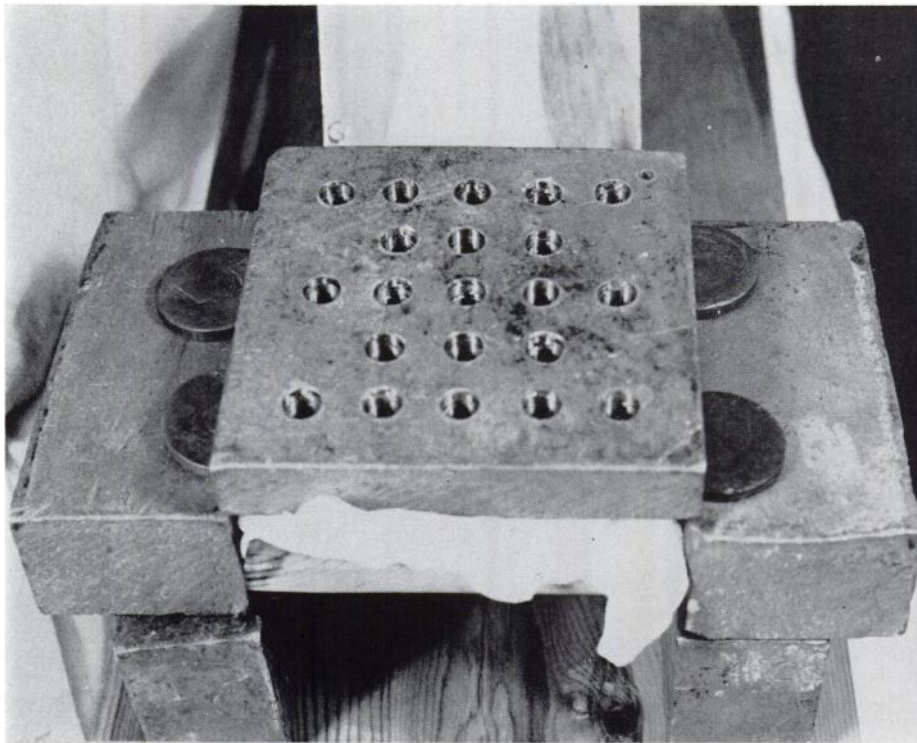

Fig. 12

of the colloidal gold (AU^{198}) which disappears from site of injection is picked up by lymph nodes within 6-12 hours. Generally, only a small amount reaches the lymph nodes in the first hour, because most of the colloidal gold (AU^{198}) is still in the segments. After exercise, concentration in femoral and inguinal lymph nodes increases greatly and pickup in iliac nodes occurs in significant amount. In some cases, lymph flow is so rapid that a large part of the material which disappears is found in the nodes in the first hour, although the patient is at rest.

Pickup by various anatomic node groups following injection of subcutaneous and intramuscular compartments in the normal lower extremity is shown in Fig. 7. The chief pathways of flow in each compartment differ somewhat, but interchange occurs. Other differences in lymph node distribution occur with diseases involving nodes and lymphatics. Also, measurement of deposition of colloidal gold (AU^{198}) is a measurement of filtration by the node. Dog and human experiments show that if colloidal gold (AU^{198}) enters a node, it remains there for at least one week which is the duration of the study. It is not known whether any of the gold is transferred out of the node later. Scintiscans, as described by us previously (3), give a picture of node pickup in the various node groups and stations (Fig. 8).

Lymph Flow Measurements in Abnormal Extremities

The technique and measurements described have been applied to a large group of patients with abnormal extremities. These are to be reported in detail, including a study of edema of varied etiology (7). Certain references are made here, however, in order to clarify the significance of some of the measurements. For example, two measurements were found to be of great value in differential diagnosis of abnormal extremities (Table II). These are 1) Disappearance rate at 24 hours and 2) Total segmental residue at 24 hours, both after subcutaneous injection.

The Disappearance Rate at 24 Hours

Disappearance rates at 24 hours from subcutaneous injection are classified into Group I, 0 to 3 per cent, Group II, 4 to 17 per cent, Group III, 18 to 39 per cent, Group IV, 40 per cent and above. Group I and II show decreased (below normal) disappearance. Group IV shows increased (above normal) disappearance. Disappearance rates within the normal range (18 to 39 per cent) may also be seen in an abnormal system when two abnormal factors are pulling in opposite direction.

Disappearance rate measures lymph flow. Lymph flow reflects the amount of lymph produced as well as the state of the lymphatics. With regard to disease states, two conditions are particularly important 1) the excess production of lymph and 2) the incompetence of lymphatics. Disappearance rate with colloidal gold (AU^{198}) is a good indicator of diseases in both categories (Fig. 2).

Increased disappearance occurs when there is increased amount of lymph produced due to differences in hydrodynamic pressures, colloid osmotic pressure and capillary permeability (8). Clinically increased disappearance (Group IV) is found in patients with edema following deep vein thrombosis and or insuffi-

ciency, cellulitis, cardiac failure and hypoprotenemia. Increased disappearance rate is also a sensitive and early indicator of increased amount of lymph. For example, increased disappearance rate (Group IV) occurs in deep vein insufficiency in the absence of edema or a history of previous edema.

Decrease in disappearance rate indicates incompetence of lymphatics. Markedly decreased disappearance rate, (Group I), specifies a diagnosis of primary diffuse lymphedema precox or severe secondary lymphedema (6). Other groupings of lymphatic insufficiency are listed in Table II, to be reported in detail.

The Presence or Absence of Segmental Residue at 24 Hours

For this measurement all segments are added together. Group A and B refer to cases with and without segmental residue at 24 hours respectively. Segmental residue in any of the segments at 24 hours is always abnormal and indicates marked interference with lymph flow. Measurements of total segmental residue at 24 hours and localization to particular segments, (a), (b), (c), (d), help define lymphatic disease states (Table II).

SUMMARY

Radioisotope techniques and methods are presented utilizing colloidal gold (AU^{198}) for studying the dynamics and functional pathways of lymph flow together with lymph node pickup and filtration function. Analysis is made of results of such study in normal extremities and disease states, such as edema.

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