

STUDIES ON PERIPHERAL BLOOD AND LYMPH FLOW UTILIZING RADIOACTIVE ISOTOPES

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Three methods utilizing radioactive materials for the studies of peripheral circulation have been reported. The first method of them was utilized by Hubbard,¹⁾ Smith, Quimby²⁾ and Wright³⁾ *et al.* This was the method trying to estimate the flow rate by measuring the velocity of blood circulation directly between two extremities. The second was carried out by Smith, Quimby,^{2) 4)} McIntyre,⁵⁾ Friedell,⁶⁾ Krieger,⁷⁾ Halligan⁸⁾ and Kumazawa⁹⁾ *et al.* When Na²⁴Cl was injected intravenously on the arm and estimated by Geiger-Muller tube on the sole, the counter value increased gradually up to maximum rate. This curve was called a build-up curve which mostly should be a constant curve in the case of normal subject. The third was done by Kety,¹⁰⁾ Elkin,^{11) 12)} Cooper¹³⁾ and Hiei¹⁴⁾ *et al.* The local sodium clearance was estimated after injection of Na²⁴Cl and this was found to serve for the diagnosis of circulation disturbance. The similar method was carried out by Mundingier,¹⁵⁾ Pabst^{16) 17)} and Lang¹⁸⁾ *et al.* using I¹³¹ instead of Na²⁴. However the above mentioned three methods were attempted for peripheral blood flow, whereas only few studies have been done for the lymphatic vessels which were said to occupy the space equal to that of the peripheral blood vessels.

Lymphangiography^{20) 21) 22) 23) 24)} has been the main clinical studies for the lymphatic vessels and even that these were only morphological studies.

For their functional studies there were only intra lymphatic pressure²⁵⁾ measurement and local clearance²⁶⁾ of radioactive iodinated human serum albumin (RISA). Experimental works using animals and humans were made to know whether RISA local clearance method was clinically useful to figure out the lymph flow, and then was studied local blood flow and lymph flow of humans and experimental dogs with peripheral vascular disturbance by the estimation of NaI¹³¹ and RISA local clearance.

THE RADIOACTIVE ISOTOPES, EQUIPMENT AND METHOD

I. The RISA and Radioactive Iodine Used for this Experimental Works

Radioactive Iodine

In this study I¹³¹ was used mainly as radioactive iodine, which was obtained from the Japan Radioactive Isotopes Association. The half-life of I¹³¹ is 8.06

days, while it is respectively 0.364 (82%), 0.28, 0.16, 0.08 Mev²⁷⁾ in case of ray energy. I^{131} is assumed to consist of 90% β ray and 10% γ ray. However, β ray reaches only 2.2 mm in tissue, so it is better to use γ ray for the estimation.

Compared with the case in which Na^{24} is used for local clearance, it is slightly more advantageous to use I^{131} , although discrimination between the two is not definite. Comparison and investigation of local clearance between Na^{24} Cl and I^{131} will be described in detail in the separate paragraph.

Radioactive iodinated human serum albumin (RISA)

About the manufacturing process of RISA, we have the reports of Aust²⁸⁾ *et al.* As elucidated by Sterling²⁹⁾ *et al.*, combined with I^{131} , RISA is considered not to change its nature chemically or immunologically different from other albumins. Furthermore, human serum albumin is 67 800 in molecular quantity and 15×3.8 m μ in size. In this study was used RISA distributed by the Japan Radioactive Isotopes Association.

II. Equipments for Estimation

Equipments for Estimating Local Clearance of Radioactive Iodine

As indicated in Fig. 1, the equipments for estimation consists of combination of three, namely, G. M. tube, rate meter and automatic recorder. G. M. tube used in this study is that of G.M. type manufactured by Kobe Industrial Company with its background 19/min, thickness of window 2.89 mg/cm², voltage for optimum action 1 310 volt.

Pulsation from G.M. tube is received by the rate meter RM 43 type manufactured by Kobe Industrial Company. This equipment enables to count average rate per second, namely, cr. p.s. to effect within six ranges of 10, 30, 100, 1 000 and 3 000. The implements is provided with a switch which can switch the probable error (%) caused from the entrance of essentially irregular radiation over those of six stages, namely, ± 0.5 , ± 1 , ± 2 , ± 5 , ± 10 and ± 20 .

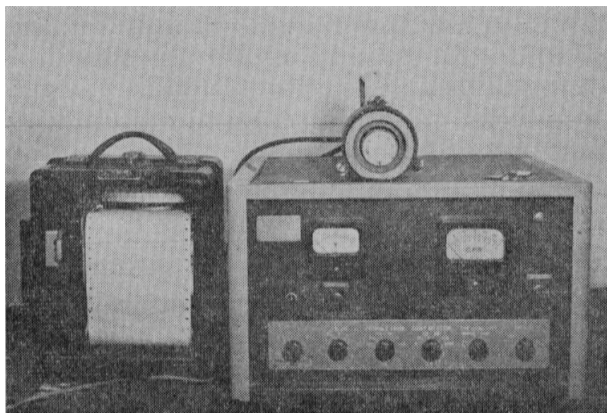


FIG. 1. Recorder. G.M. tube. Ratemeter.

The automatic recorder is D-100 type made of Yokogawa Electric Apparatus Mfg. Company. The speed of record paper's transmission is controlled by changing the combination of gears.

Equipments for Estimating RISA Local Clearance

As indicated in Figure 2, scintillation probe connected with a counter is used for estimation. The scintillation probe is suitable for estimation, as it is as much as 150 times effective for γ ray, compared with G.M. tube. The scintillation probe used in this study is PS-1 B type made by Kobe Industrial Co. The counter is SA-1000 C type made also by the said company with voltage for optimum action 1250 volt and the background 131/minute.

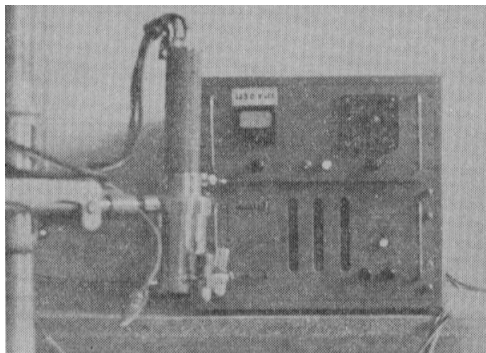


FIG. 2. Scaler. Scintillation probe.

Equipment for Estimation Used in the Fundamental Animal Experiments

In the case of canine experiments, local clearance of both NaI^{131} and RISA was administered with the same equipments for estimation as used clinically under the same conditions as possible as above noted.

However, in the animal experiments which needed the collection of samples, was used a well-type scintillation counter made by Kobe Industrial Company. Comparing to the method to use a dish, the well-type counter is very convenient in γ ray estimation which can be done by just putting fluid into the special testing tube. The equipment for estimation used in this study is the scintillation probe-PS-2 B type of Kobe Industrial Company to which a scaler is connected. The scaler is SA-1000 C type made by Kobe Industrial Company with voltage for optimum action 1250 volt, the background 365/min.

III. The Method of Estimation

The Method of Estimating Radioactive Iodine Local Clearance

After NaI^{131} was diluted with physiological saline, it was injected subcutaneously on the leg. The subcutaneous space instead of intramuscular space was chosen to save the radioactive materials. The injected quantity was 0.2 cc 10 μc .

The method for estimation is shown in Fig. 3. In this case, at the front of the mica window of G.M. tube is attached an aluminium plate 540 mg/cm² in order to protect the entrance of β ray, as ascertained by Ito.³¹⁾ Moreover, G.M. tube except the window was covered with a lead shield 2 cm in thickness in order to protect the γ ray radiation. Pulsation entered into G.M. tube like

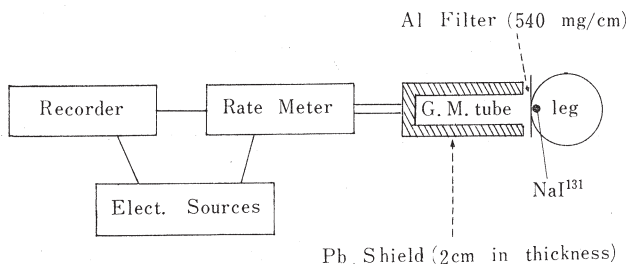


FIG. 3. NaI¹³¹ local clearance.

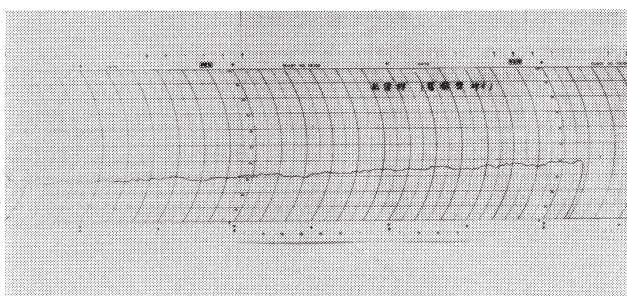


FIG. 4. NaI¹³¹ local clearance curve (normal person)
case 15 Male 25 ys.

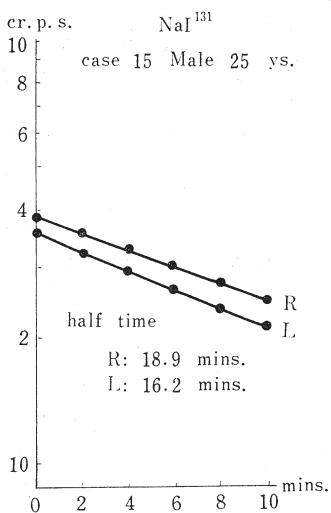


FIG. 5. NaI¹³¹ local clearance (normal person).

this, is indicated as the cr. p. s. variation on the rate meter directly connected, which is automatically recorded in the automatic recorder. The speed of record paper transmission was fixed as 40 mm per minute.

Fig. 4 indicates the NaI¹³¹ clearance curve of a normal person automatically recorded by the above method. The record paper showed from the right to left how cr. p. s. was decreased. If the clearance curve is drawn on the half-logarithmic table, or cr. p. s. in contrast to the time, it will be linear as shown in Fig. 5. This will completely agree with the theory of local clearance asserted by Ketty. Consequently, K. value will be as follows:

$$K = \frac{\log cr_1 - \log cr_2}{0.4343(T_2 - T_1)}$$

Providing, however, cr₁ cr₂ are assumed respectively, cr. p. s. at T₁T₂ (minute).

However, what is called biological half time (T 1/2) by Veall,³²⁾ namely,

the time needed in which the initial radioactivity reduces into half after estimating clearance is always constant as in the following equation, therefore, this half time was used in this study.

$$\frac{\log cr_1 - \log cr_2}{T_2 - T_1} = \frac{\log cr_x - \log cr_x/2}{T_{1/2}} = \frac{\log 2}{T_{1/2}}$$

$$T_{1/2} = \frac{(T_2 - T_1) \log 2}{\log cr_1 - \log cr_2}$$

provided, However, cr_1 , cr_2 , cr_x are assumed respectively to be cr. p.s. at T_1 , T_2 , x (minute).

This is meant essentially to be same as K value, but, different from the latter, it can be represented by time with the advantage for easier understanding in general. Therefore, as the local effective blood circulation quantity increases, K value becomes larger but half-time becomes shorter. Vice versa, if the local effective blood circulation quantity reduces, K value becomes smaller, while the half-time becomes longer. Further, $T_2 - T_1$ is desirable to be at least more than 10 minutes.

The Method for Estimating RISA Local Clearance

Like NaI^{131} local clearance the estimation is made on the leg. The part is marked with a dermatopencil beforehand. (This is because the estimation is not continuous as RISA local clearance but done at a certain interval of time, so it requires always to estimate the same region.) RISA will be diluted with physiological saline which 0.2 cc is to be $10 \mu c$ and injected subcutaneously on the marked spot.

Also, if the injected contents of radioactive materials exceeds 1.0 cc, it would be unphysiological. For this reason, the injected quantity of radioactive materials must be always the same, otherwise we may loose the ground to compare the circulation of blood with that of lymph on the site.

Dosage needs not strictly be constant since the local clearance depends on the reduced quantity of radioactive materials on the site, but it is better to be constant as possible. Mundinger¹⁵⁾ suggests that 6 to $10 \mu c$ is most suitable. Compared with muscular injection, hypodermic injection can do with less amount of injection and radioactivity which will result in the less distur-

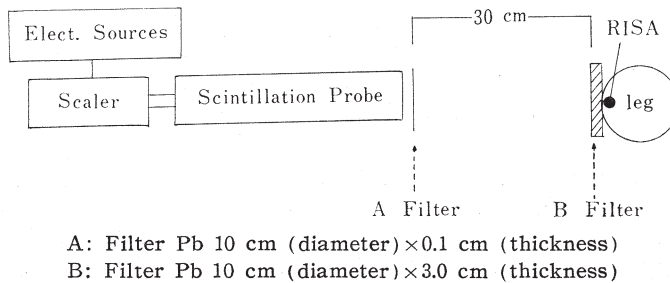


FIG. 6. RISA local clearance.

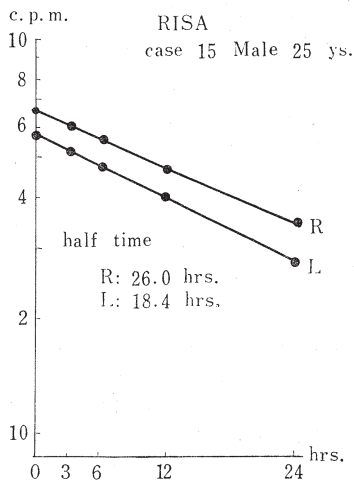


FIG. 7. RISA local clearance (normal person).

bance in tissues by the latter way of injection.

Issues on the Subjects

In case of estimating subjects, it is desirable that all conditions are to be same as possible. It might be impossible to make them exactly same, so we should be careful to have them same as possible in order to lessen the possible error in estimation.

The room should be quiet with its preferable ambient temperature of 20°-25°C. The local circulation will vary depending on the mental state of the subject, so it is necessary to explain him beforehand that the experiment is quite harmless, and painless in order to get his cooperation. Due to the movement in

the location, the state of circulation will also vary. Accordingly, the subject must take rest at least for half an hour in the estimation room before the experiment starts. During the estimation, the position of body should be horizontal.

FUNDAMENTAL ANIMAL EXPERIMENTS BY USING DOGS

As experimental animals, we used the healthy adult dogs with the weight between 10 and 20 kgs. For anesthesia thiamylal was used intravenously or intraperitoneally in all cases.

I. Fundamental Experiment by Normal Dogs

The Method

Eight adult dogs were selected and rightly fixed on the horizontal spinal position. After opening left side of the neck, thoracic duct was ligated at the joint of v. subclavia sinistra and v. jugularis sinistra causing expansion of thoracic duct, then polyethylene tube with 1 mm diameter was inserted to the thoracic duct and the other end of this tube was brought on the outside of bodies. V. femoris was exposed in order to ease the blood collection. For anesthesia, thiamylal of 20 mg/kg was injected intravenously and added if necessary, so that the anesthesia could be maintained to keep respiration at 10-15/min.

This is to protect the lymph flow to be influenced from the respiration movement of 8 adult dogs thus treated, 4 dogs were injected subcutaneously on the lower leg with NaI^{131} 0.2 ccm 10 μc in order to examine the local clearance of an radioactive iodine, whereas the remaining 4 dogs were injected subcutaneously on the same site with RISA 0.2 ccm 10 μc to investigate RISA local

TABLE 1. NaI¹³¹ Local Clearance of Normal Person
(Gastrocnemius Muscle)

Male				Female			
Case (No.)	Age (y. r)	Half time (mins)		Case (No.)	Age (y. r)	Half time (mins)	
		R	L			R	L
1	23	16.5	15.4	7	42	28.1	17.2
2	38	12.1	19.8	8	26	16.1	18.2
3	25	13.1	12.7	9	37	13.4	15.9
4	40	16.0	14.2	10	20	10.1	10.7
5	21	11.3	10.5	11	30	15.0	16.2
6	34	15.9	14.1				
Average		14.2	14.5	Average		16.5	15.6
		14.3				16.1	
Total average		15.1					

TABLE 2. Muscle Local Clearance of Inorganic Radioisotopes (Gastrocnemius Muscle)

Name	Inorganic radioisotope	Kety value	half time (mins)
Hiei	Na ²⁴	0.0541	12.8
Kety	Na ²⁴	0.050	13.9
Cooper	Na ²⁴	0.050	13.9
Reese	Na ²⁴	0.040	17.3
Mc. Girr	Na ²⁴	0.055	12.6
Pabst	I ¹³¹	0.0456	15.4
Narita	I ¹³¹	0.0459	15.1

clearance.

Later, we collected lymph intermittently through the polyethylene tube inserted into the thoracic duct as well as the blood from v. femoralis on the side of leg in which radioactive materials were injected. Then, these were estimated by the well-type scintillation counter.

Local clearance of the NaI¹³¹ was examined of the 4 dogs. A clearance curve was sought for two dogs at the same time by similar method of estimation to that done for the human subject.

Eight adult dogs were taken as controls, and were estimated for NaI¹³¹ as well as RISA local clearance in the exactly same manner as done to humans.

The Result

1. Group Used NaI¹³¹

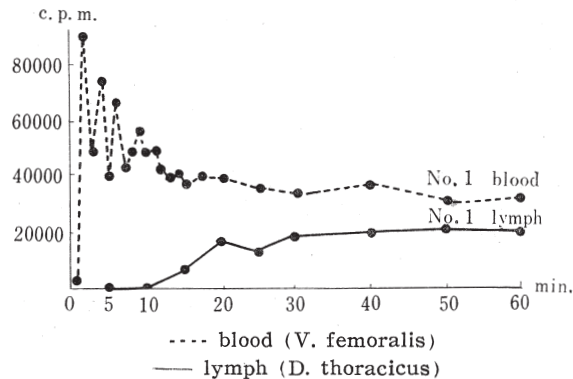
From two dogs were respectively collected their lymph and blood for one hour, while from other 2 dogs for two hours. The quantity of lymph and blood collected each time was 1.0 ccm respectively.

Table 3 is the result of estimation. The counter values in the table were deducted average of the background before, during and after the estimation.

Fig. 8 is the diagram representing one example of these. As we can see

TABLE 3. NaI¹³¹ Local Clearance of Normal Dogs

Time (min)	Count				Time (min)	Count			
	No. 1		No. 2			No. 3		No. 4	
	Blood	Lymph	Blood	Lymph	Blood	Lymph	Blood	Lymph	
1	3737		48854		2.5	40531		5760	
2	89729		101151		5	28747	184	3871	26
3	48299		103690		7.5	35433		2957	
4	74079		83486		10	35936	5942	3840	53
5	39768	8	81557	20	12.5	28816		2231	
6	69376		68407		15	27132	7901	2750	50
7	43433		71804		17.5	26757		2552	
8	49260		72265		20	19838	10001	2795	1605
9	57147		66976		25	24411	9554	2444	1650
10	48939	67	53720	896	30	21967	11554	2183	1542
11	49141		56927		40	18659	12097	1960	1880
12	42769		50851		50	13669	12659	1818	1798
13	40194		50056		60	11260	12013	1902	1816
14	41592		39862		75	12861	12580	1675	1783
15	37744	7227	42359	17922	90	11610	11617	1448	1894
17.5	41789		40407		105	11809	11585	1567	1619
20	39225	15895	38404	20048	120	11518	10489	1516	1739
25	36169	13701	34762	19427					
30	34714	17642	36934	18129					
40	38334	19924	33041	19437					
50	32076	21868	21709	16714					
60	32369	21830	23880	17842					

FIG. 8. NaI¹³¹ local clearance (normal dog)

by these tables and figures, even one minute after the injection large dosage of radioactive materials begins to appear in the blood, while it will take 5 to 15 minutes before the same materials appear in the lymph. About 30 minutes later, the radioactive materials in both lymph and blood would reach to the balanced state. If examined in further detail, it does not follow that the counter value in blood decreases linearly in reaching the balanced state, showing remarkable variations in the way.

We can attribute this to the coincidence between the radioactive materials

circulating through the body after their absorption from the subcutaneous space and those absorbed directly from the same space.

The balancing state is derived because radioactive materials become uniform in the whole blood circulating through the body. It is sometimes seen that the counter value of lymph sample exceeds that of blood sample. This does not mean that more radioactive materials are absorbed by the lymph than by the blood.

Since there is much difference in circulating quantity between the lymph and the blood, the total radioactive materials in the blood are remarkably much in quantity.

The half-time for 5 dogs of which clearance curve was sought is such as shown in Table 4. In No. 1 and No. 2, clearance curve was sought while taking samples from the thoracic duct and v. femolaris. Fig. 9 is the clearance curve of No. 1 recorded in the automatic recorder. Fig. 10 represents this drawn on half-logarithmic table. As for 5 dogs, the average half-time was 15.6 minutes and no noticeable difference was recognized between the left and right side.

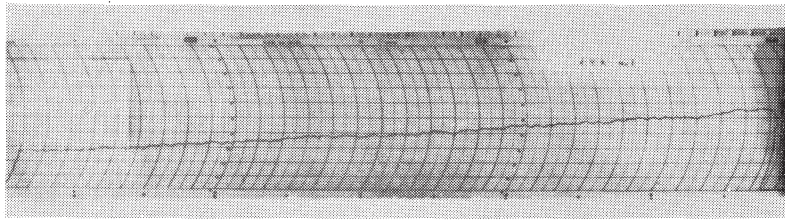


FIG. 9. NaI¹³¹ local clearance curve (normal dog)

TABLE 4. NaI¹³¹ Local Clearance of Normal Dogs

Case (No.)	Half time (mins.)	Measured side (leg. subcutane.)
1	16.4	L
2	9.2	L
9	13.1	R
10	19.3	R
11	20.1	R
Average	15.6	

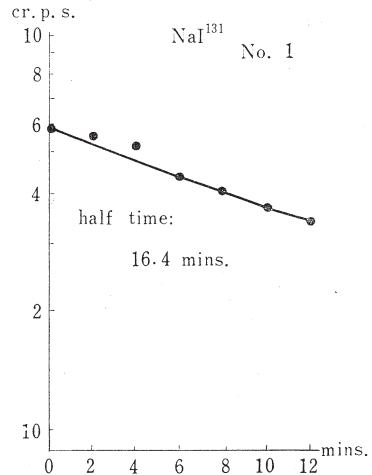


FIG. 10. NaI¹³¹ local clearance (normal dog).

2. Group used RISA

Extending over six hours were collected lymph from the polyethylene tube inserted into the thoracic duct and blood from v. femoralis. The collected quantity was respectively 1 ccm.

Table 5 shows the true counter value from which was deducted. As seen from the table, 4 dogs experimented were all found with little radioactive materials appeared in the lymph after one hour to three hours and had a trend to increase even after six hours. Fig. 11 is the indication of the result of experiment in diagram which represents the above fact.

Table 6 indicate half-time of 5 dogs from which clearance curves were sought. The average half-time was 21.7 hours.

Table 7 shows one example of the counter values in which RISA local

TABLE 5. RISA Local Clearance of Normal Dogs

Time	Count							
	No. 5		No. 6		No. 7		No. 8	
	Blood	Lymph	Blood	Lymph	Blood	Lymph	Blood	Lymph
5'	17	11	20	1	20	10	19	18
10'	28	0	4	4	65	0	38	0
20'	24	13	17	10	21	0	21	11
30'	51	24	10	15	16	13	19	13
45'	50	35	13	5	31	39	33	40
1°00'	19	0	27	3	24	40	18	11
1°30'	28	0	14	7	12	685	17	44
2°00'	10	80	50	12	10	2217	50	52
2°30'	9	21	12	16	21	4878	54	131
3°00'	26	1029	96	492	10	7319	37	28
3°30'	20	1774	23	1011	17	8818	50	1076
4°00'	15	2535	11	1998	31	10365	10	1659
4°30'	39	3367	19	5583	43	10913	45	2599
5°00'	27	3835	18	8402	15	11399	51	2870
5°30'	24	5855	29	9992	29	12359	61	3631
6°00'	50	6552	30	10480	56	13245	62	4074

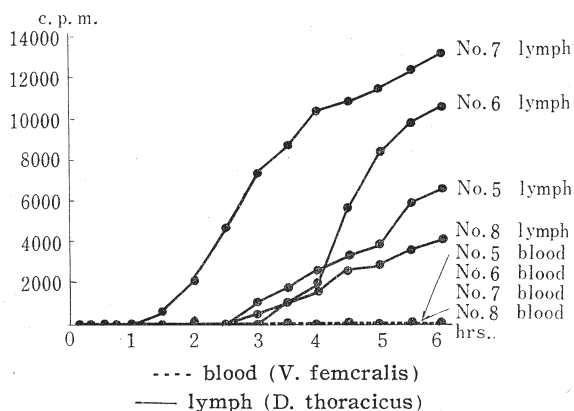


FIG. 11. RISA local clearance.

TABLE 6. RISA Local Clearance of Normal Dogs

Case (No.)	Half time (hrs.)	Measured side (leg. subcutane.)
12	28.2	L
13	23.4	R
14	18.3	R
15	22.6	L
16	16.2	L
Average	21.7	

TABLE 7. RISA Local Clearance of Normal Dog (No. 3)

Measurement	Count.
immed. after injection	4693
3 hrs. after	4353
6 hrs. after	3905
12 hrs. after	3251
24 hrs. after	2249

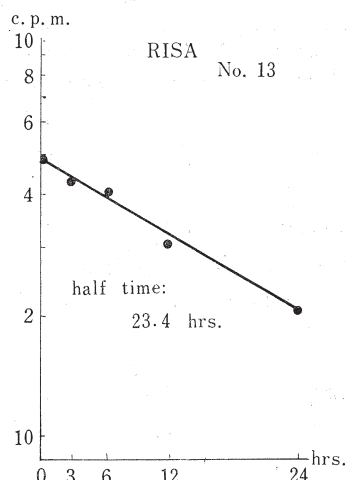


FIG. 12. RISA local clearance (normal dog).

clearance was estimated in terms of hours. Fig. 12 is the representation of this drawn on the half logarithmic table, which shows that, if the counter value is drawn on the half-logarithmic table in contrast to the time, then the former becomes straight line.

II. Local Clearance at Arterial Occlusion Caused by Arterial Thrombosis

The Method

Eight normal adult dogs were induced thrombosis of arteries for experiment. A. iliaca externa on one side is isolated and after its ligation, A. femoralis on same side was also exposed and ligated. In the meantime, thrombin 500 unit manufactured by Mochida pharmaceutical Company is resolved in 5 ccm physical saline and 2.5 ccm—250 unit— was injected into the artery between above noted 2 ligations. Thus, thrombosis was induced in the arteries between A. iliaca externa and A. femoralis and their branches.

After three to five hours from such operation, the estimation for RISA local clearance was started both on the operated and the non-operated side. On the following day the NaI¹³¹ local clearance was estimated by the dogs undergone similar operations.

The Result

The result of the estimation is shown in Table 8. Average half-time for NaI¹³¹ local clearance was 86.3 minutes on the operated side and 22.3 minutes on the non-operated side, whereas average half-time for RISA local clearance was 34.4 hours on the operated side and 25.1 hours on the non-operated side. Both local clearances were recognized to be retarded on the operated side.

TABLE 8. Local Clearance of Arterial Thrombosis (dog)

Case (No.)	Half time NaI ¹³¹ (mins.)		Ope side	Case (No.)	Half time RISA (hrs.)		Opeside
	Ope side	Non-ope side			Ope sides	Non-ope side	
17	76.0	35.6	R	21	49.3	35.7	R
18	58.3	16.8	R	22	28.2	26.4	R
19	128.4	12.1	L	23	27.6	20.1	R
20	82.5	24.6	L	24	32.5	18.0	L
Average	86.3	22.3		Average	34.4	25.1	

Ope side: operated side

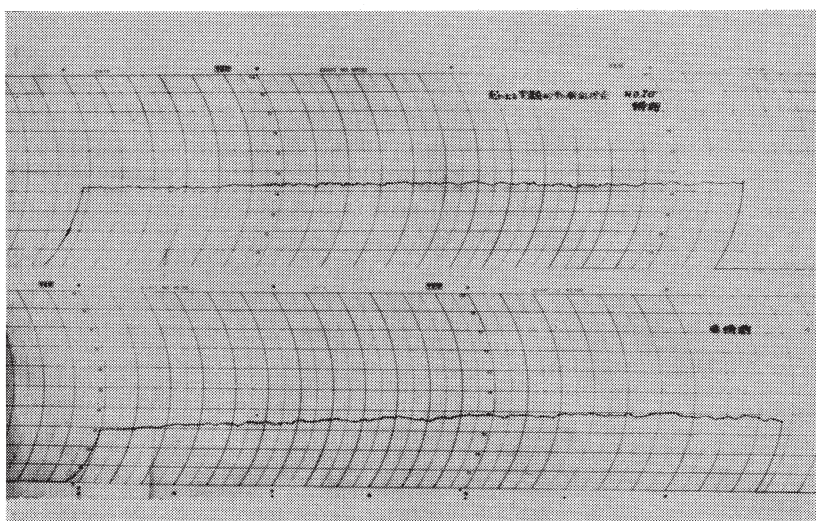
Non-ope side: non-operated side

Fig. 13 is the record of NaI¹³¹ in the automatic recorder. If NaI¹³¹ and RISA local clearance curves are drawn on the half-logarithmic table in contrast to the time, each of the two local clearance is retarded on the operated side (Fig. 14).

III. Local Clearance at Venous Occlusion Caused by Venous Thrombosis

The Method

For experiment 10 adult dogs were used. V. iliaca externa was isolated and ligated, then v. femoralis on the same side was exposed and ligated as well. During all this time, in order to induce the thrombosis surely in the vein, Mochida pharmaceutical Co., Ltd.'s product, thrombin 500 μ was resolved with 5 ccm of physiological saline and 2.5 ccm (250 μ) was injected into the vein between above noted ligations. Of half of dogs treated above, Eli, Lilly's



upper: operated side lower: non-operated side

FIG. 13. NaI¹³¹ local clearance curve of Arterial Thrombosis (dog)

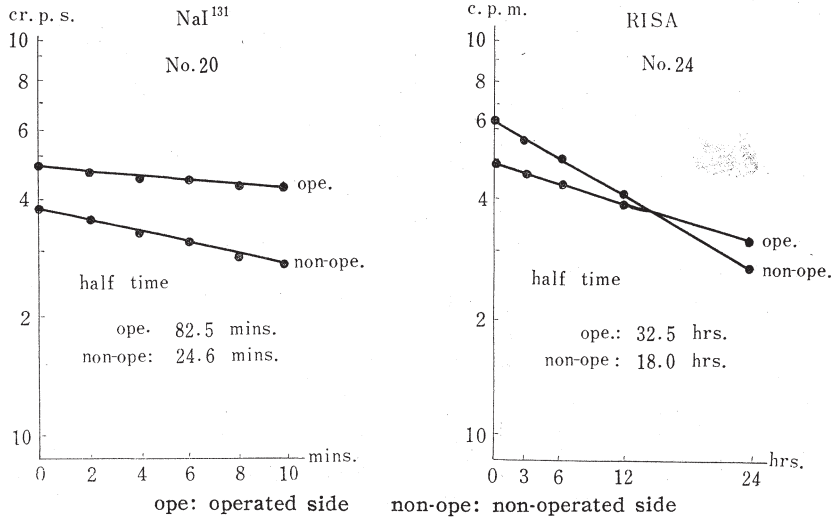


FIG. 14. Local clearance of Arterial Thrombosis (dog).

5% morrhuate sodium 1.5 ccm was injected into the veins.

After such operation edema became remarkable on the leg on the operated side within one to two hours, so the estimation of RISA local clearance was started three to five hours after operation. On the following day the NaI¹³¹ local clearance was estimated by the dog 24 hours after their operation.

The Result

The result of estimation for both clearances of NaI¹³¹ and RISA were

TABLE 9. Local Clearance of Venous Thrombosis (dog)

Case (No.)	Half time NaI ¹³¹ (mins)		Pressure of V. Saphena (mmH ₂ O) 24 hrs after operation		Ope side
	Ope side	Non-ope side	Ope side	Non-ode side	
25	48.2	18.3	280	75	R
26	158.4	32.0	345	80	R
27	46.6	12.1	260	75	R
28	243.6	26.2	300	90	L
29	56.8	19.4	270	120	L
Average	110.7	21.6			
Case (No.)	Half time RISA (hrs.)				
	Ope side	Non-ope side			
30	14.1	29.6	270	90	R
31	17.8	18.8	270	115	L
32	18.1	35.4	255	85	L
33	14.0	14.4	305	100	L
34	16.9	21.3	275	95	R
Average	16.2	22.2	283	93	

Ope side: operated side

Non-ope side: non-ope ratedside

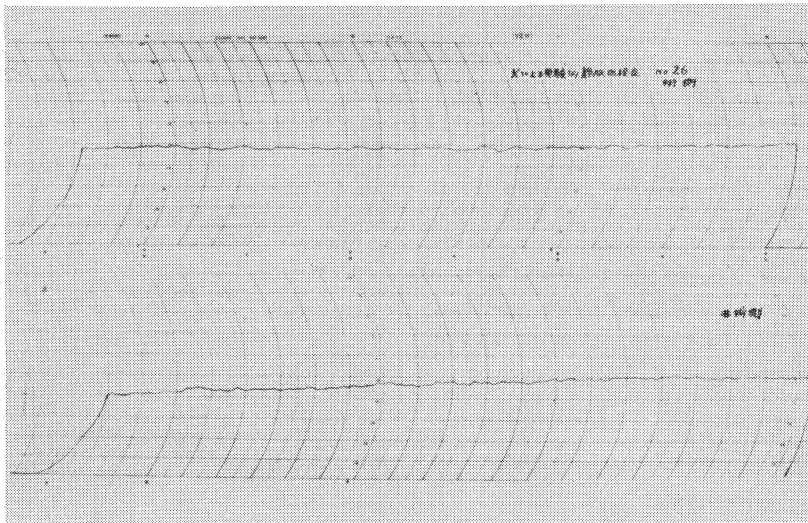
shown in Table 9. Average half-time for local clearance of NaI^{131} was 110.7 minutes on the operated side and 21.6 minutes on the non-operated side, a remarkable retardation was noticed on the former. The average half-time for RISA local clearance was 16.2 hours on the operated side and 22.2 hours on the non-operated side. Of the five dogs, a remarkable promotion on the operated side was noted for three dogs and a slight promotion for the remaining two.

Further, about each case, pressure of saphenous vein and circumference of the leg was measured. As shown in Table 9, the venous pressure was counted 190 mm H_2O in average on the operated side which was higher on the non-operated side.

As shown in Table 10, average circumference of the leg has shown more

TABLE 10. Circumference of Leg (Venous Thrombosis of Dogs) (cm)

Case (No.)	Operated side			Non-operated side			Operated side
	Leg	Knee	Thigh	Leg	Knee	Thigh	
25	12.9	19.5	24.5	11.5	18.0	22.0	R
26	12.5	20.5	26.0	12.0	18.2	23.5	R
27	9.0	19.5	26.0	8.0	18.0	24.5	R
28	12.0	20.5	25.0	11.0	19.0	23.0	L
29	8.5	17.0	21.5	7.0	15.0	19.0	L
30	11.6	17.2	23.0	9.6	15.5	20.5	R
31	11.5	20.5	29.5	8.5	17.0	24.0	L
32	11.0	16.5	21.2	8.0	14.5	18.5	L
33	12.0	19.2	24.5	11.5	18.0	22.0	L
34	12.8	20.0	25.5	10.5	18.5	23.5	R
Average	11.3	19.0	24.7	9.8	17.2	22.1	



upper: operated side lower: non-operated side
 FIG. 15. NaI^{131} local clearance curve of Venous Thrombosis (dog).

swelling on the operated side by 1.5-2.6 cm than on the non-operated side. Moreover, circumference of the leg was measured at three points, namely, the part of the thigh 5 cm above the knee joint, at the knee, and middle part of the lower leg.

Fig. 15 is the NaI^{131} local clearance recorded in the automatic recorder. In Fig. 16 two local clearance curves of NaI^{131} and RISA were drawn on the half-logarithmic table in contrast to the time. Compared with the non-operated side, the operated side local clearance of curve was slow in inclination, whereas RISA local clearance inclines more sharply.

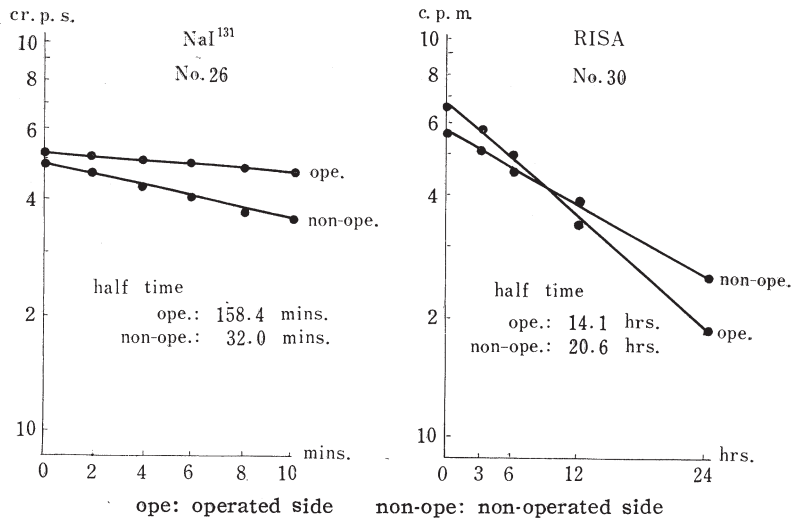


FIG. 16. Local clearance of Venous Thrombosis (dog).

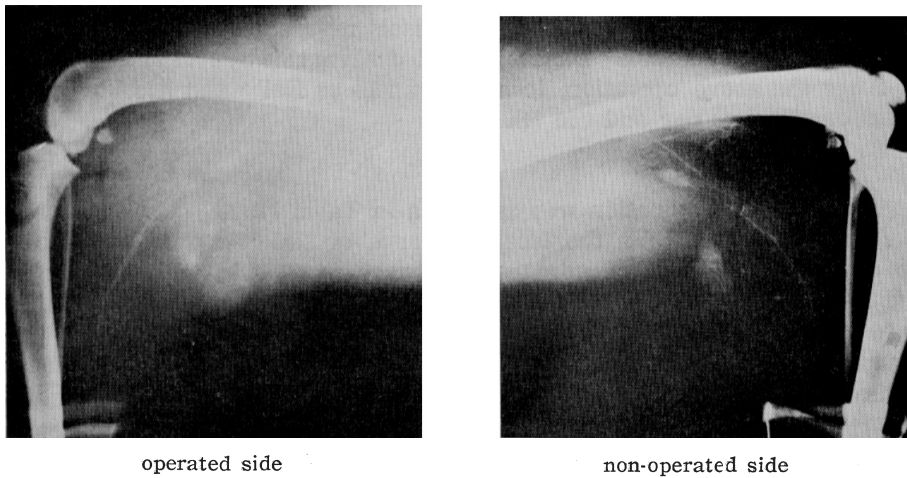


FIG. 17. Lymphangiography of leg by Danese's method (experimental dog of Venous Thrombosis)

Fig. 17 is the lymphangiograph of the experimental dog induced thrombosis of the veins. By this we can see that, compared with non-operated side, the operated side has more swollen lymphatic vessels. In taking the dog's lymphangiograph, the method of Danese, C⁽⁴²⁾ was adapted.

By the venography of dog in Fig. 18, the thrombosis of v. femoralis is demonstrated.

IV. Local Clearance at Lymphedema

The Method

By the same method with those of Halsted⁽⁴³⁾ Reichert,⁽⁴⁴⁾ 12 adult dogs were induced experimental lymphedema.

After anesthesia of the dogs with thiamylal, 0.5 ccm of skyblue or 2 ccm of Evans blue was injected subcutaneously on the leg to cause lymphatic edema. About 30 minutes after the pigment injection, operation was started.

This was designed to dye the lymphatic vessel of the leg on its operated side with pigment, sky or Evans blue. An incision surrounding the thigh was made muscle, fascia, lymphatic vessels and soft tissues, however, main blood vessels were not amputated. Edema on the operated side developed gradually to the maximum about one week after the operation. From that time, edema started to disappearance and recovered completely three or four weeks later. From this we may assume that lymph vessels regenerate about three or four weeks after the operation. Danese⁽⁴⁵⁾ *et al.* confirm this by lymph angiography.

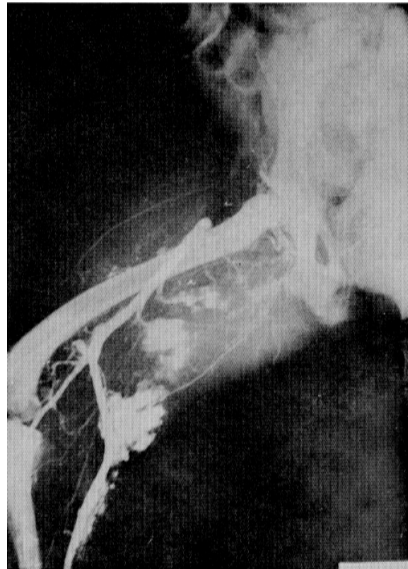
After the above operation, local clearances of NaI¹³¹ and RISA were estimated on the first day and the 7th day.

The Result

The result of estimation was as shown in Table 11.

Average half-time for the local clearance of NaI¹³¹ was 29.0 minutes on the operated side and 22.5 minutes on the operated side with the trend of slight retardation. Probably this is because the small vessels in the subcutaneous space and muscular layer is amputated in operation. This can be considered from the fact that the NaI¹³¹ local clearance was noted remarkable retardation on the first day of operation but not so much 7 days after operation.

When RISA local clearance on the operated side was observed on the first day of operation, RISA was not absorbed almost at all from operated side, that is, average half-time is infinite. However, on the 7th day, out of four cases, one is infinite, whereas in other three cases was shown a remar-



operated side

FIG. 18. Venography of V. Saphena (experimental dog of Venous Thrombosis).

TABLE 11. Local Clearance of Lymphedema (Dog)

Case (No.)	Half time NaI ¹³¹ (mins.)		Measured day after ope	Ope side
	Ope side	Non-ope side		
35	30.4	25.6	1	R
36	39.2	26.1	1	L
37	27.6	12.8	7	L
38	24.2	27.7	7	L
39	23.8	20.1	7	R
Average	29.0	22.5		

Case (No.)	Half time RISA (hrs)			
	Ope side	Non-ope side		
40	∞	30.1	1	R
41	∞	41.3	1	L
42	∞	24.2	1	R
43	188.1	28.5	7	R
44	87.6	13.0	7	L
45	∞	22.7	7	L
46	65.4	18.7	7	R
Average		25.5		

Ope side: operated side
 Non-ope side: non-operated side

TABLE 12. Circumference of Leg (Lymphedema of Dogs) (cm)

Case (No.)	Operated side			Non-operated side			Operated side
	Foot	Leg	Knee	Foot	Leg	Knee	
37	9.5	14.0	20.5	8.0	9.0	16.5	L
38	10.5	12.0	20.0	9.0	10.5	18.0	L
39	9.5	13.5	23.0	7.5	8.0	14.5	R
43	9.0	10.0	18.5	7.0	7.5	14.0	R
44	10.0	13.0	19.5	9.0	10.0	16.0	L
Average	9.7	12.5	20.3	8.1	9.0	15.8	

kable retardation in half-time. On the other hand, average half-time of RISA local clearance on the non-operated side was 25.5 hours being nearer to normal.

As shown in Table 12, at the estimation one week later, the circumference of the leg indicated more remarkable swelling on the operated side than the non-operated side. Compared with the non-operated side, average circumference of the leg was larger from 16 cm to 4.5 cm. The estimation was conducted at those sites, namely, at the knee joint, leg and foot.

Table 13 concerns the pressure of the saphenous vein seven days after operation. On the operated side it was 148 mm H₂O in average and 93 mm H₂O on the non-operated side, the former being somewhat higher. However, compared with the experimental thrombosis in vein, the vein pressure was remarkably lower.

Fig. 19 is the venography obtained with injection of contrast medium

TABLE 13. Pressure of V. Saphena
(Lymphedema of Dogs) (mmH₂O)
Lweek After Operation

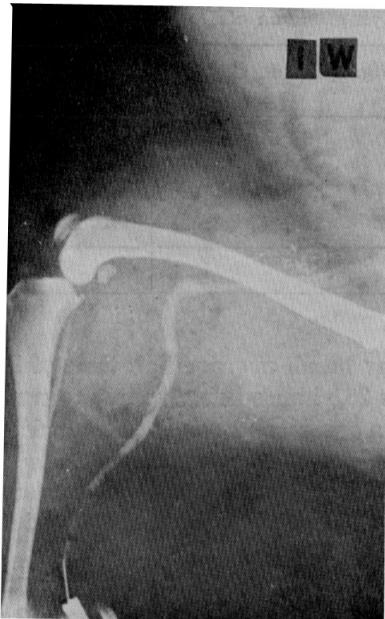
Case (No.)	Operated side	Non-operated side	Operated side
37	160	100	L
43	140	90	R
44	145	90	L
Average	148	93	

rated side. From this it is also demonstrated that edema caused by this operation was of lymphatic nature.

In Fig. 21 is indicated the NaI¹³¹ local clearance after seven days from the operation recorded in the automatic recorder. Compared with non-operated side, the operated side bears a slight trend of retardation but light in degree.

Fig. 22 is local clearance curves of NaI¹³¹ and RISA drawn on the half-logarithmic table in contrast to the time. Compared with non-operated side, the operated side had RISA local clearance curve with very slow inclination being horizontal to the fundamental line, and this showed the insufficient absorption of RISA from the local tissue. In case of NaI¹³¹ local clearance,

from the saphenous vein on the operated side. As we can see from this, no thrombosis in the vein was recognized. Fig. 20 is the lymphangiography (after Danese's method) seven days after the operation of the leg. According to this, on the seventh day after the operation, the lymph trunk was thoroughly amputated at the operated side.



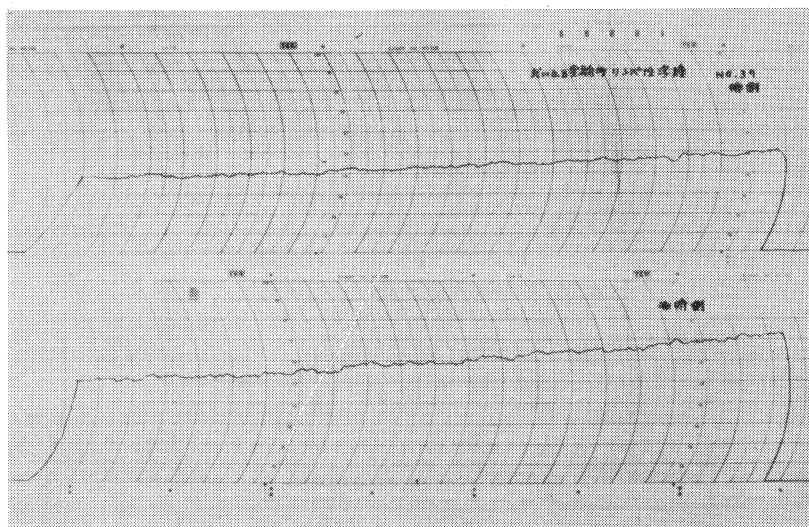
operated side

FIG. 19. Venography of V. Saphena
(experimental dog of Lymphedema).



operated side 1 week after operation

FIG. 20. Lymphangiography of
leg by Danese's method.
(experimental dog of Lymphedema)



upper: operated side lower: non-operated side

FIG. 21. NaI¹³¹ local clearance curve of Lymphedema (dog).

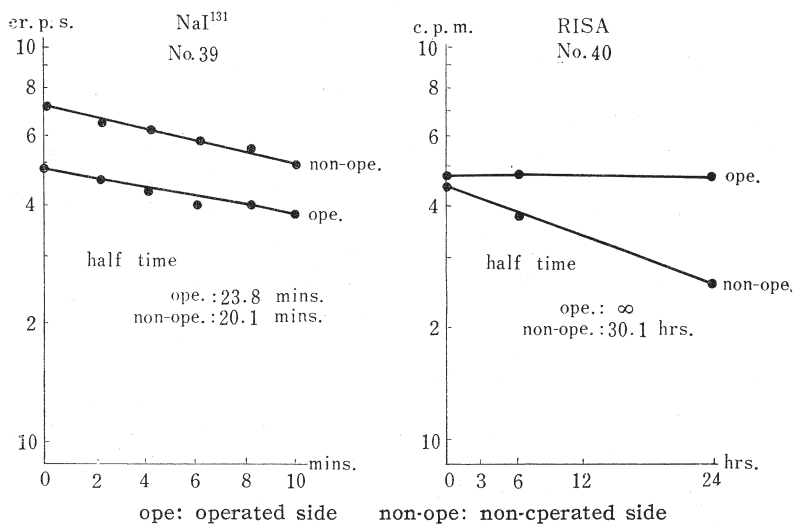


FIG. 22. Local clearance of Lymphedema (dog).

inclination of the curve was almost similar on the operated and non-operated sides, which shows that the blood flows was not so much disturbed on the operated side.

V. Discussion

By the experiments of normal dogs, it was revealed that NaI¹³¹ local

clearance mainly concerned with the blood flow but did not play any significant role on the lymph flow.

This agrees well with the report of Stone⁴⁶⁾ in his study of Na²⁴ movement from dog's gastrocnemius that, only less than 1.1% of the injected contents shifts in to the thoracic duct and the lymph flow does not show to be any important factor to the local clearance.

On the other hand, RISA local clearance mainly concerns with the lymph flow but the blood flow performs no significant role. As for RISA's permeability into the capillary blood vessel and its transudation from the lymphatic duct, more details will be explained later.

In the experimental dogs induced in thrombosis of the arteries, both local clearances of NaI¹³¹ and that of RISA are retarded on the operated side showing disturbance of blood and lymph flows.

Irisawa⁴⁷⁾ followed up the biological microscopic observation of the lymph vessels of a frog and admitted that, if A. femoralis is oppressed, the velocity of lymph flow is remarkably retarded at the leg. As seen in this report, we can assume that the oppression of arteries will influence on the lymph flow too.

In the edema caused by the experimental thrombosis in veins, the NaI¹³¹ local clearance is retarded. Meanwhile, RISA local clearance tends to be promoted on the operated side. This may be interpreted that, because of the disturbed venous blood flow on the operated side, lymph flow tends to be promoted in compensation to a certain extent.

This is also endorsed by lymphangiography that the lymphatic vessel swells on the operated side to promote the lymph flow. In case of experimental lymphatic edema, RISA local clearance was noticeably retarded. Especially, on the first day of operation, RISA was not absorbed from the local tissue at all. However, on the seventh day, it had a more or less tendency for regeneration. As for NaI¹³¹ local clearance on the first and seventh day after the operation, compared with non-operated side, there was a tendency of retardation on the operated side but its degree was slight.

CLINICAL RESULTS

Both local clearances of NaI¹³¹ and RISA was estimated subcutaneously at the leg of normal subject, the patients with disturbance of peripheral circulation and the patients before and after getting lumbal sympathectomy or adrenalectomy.

I. Normal Persons

The Result

The result of estimation for fourteen normal subjects are shown in Table 14. The half-time NaI¹³¹ local clearance was within the range of 32.8 minutes at the highest and 13.8 minutes at the lowest, average value being 22.0 minutes. According to sex distinction, average half-time for 7 men were 22.2 minutes, while that for 7 women were 21.7 minutes showing no significant difference

TABLE 14. Local Clearance of Normal Persons

Male					Femal						
Case (No.)	Age (y. r)	Half time				Case (No.)	Age (y. r)	Half time			
		NaI ¹³¹ (mins.)		RISA (hrs.)				NaI ¹³¹ (mins.)		RISA (hrs.)	
		R	L	R	L			R	L	R	L
12	38	24.0	27.2	18.1	13.4	19	20	13.8	14.8	13.5	13.4
13	21	21.7	22.4	10.2	11.4	20	35	16.3	15.2	16.2	18.0
14	23	26.2	25.5	30.1	26.3	21	26	20.1	22.3	28.1	23.2
15	25	18.9	16.2	26.0	18.4	22	31	20.3	27.7	17.1	15.4
16	29	15.7	17.3	20.3	16.6	23	30	32.8	31.7	21.3	20.1
17	40	30.0	26.1	14.1	18.4	24	42	24.4	26.3	22.3	20.4
18	34	20.6	19.5	24.8	23.3	25	37	18.0	21.7	24.2	26.1
Average		22.4	22.0	20.5	18.3	Average		20.7	22.8	20.1	19.5
		22.2		19.4				21.7		20.0	

Total average NaI¹³¹ local clearance 22.0 mins.

RISA local clearance 19.7 hrs.

between the two.

Half-time for RISA local clearance was 30.1 hours at highest and 10.2 hours at lowest with average value of 19.7 hours. According to sex distinction, average half-time for 7 men was 19.4 hours whereas that for 7 women was 20.0 hours. Average half-time was 20.3 hours for right and 18.9 hours for left with no significant difference between the two for both sex.

Discussion

Average half-time for NaI¹³¹ local clearance was 22.0 minutes which was quite similar to 21.7 minutes (K value 0.0314) of Hiei's report. Pabst¹⁷⁾ estimated NaI¹³¹ local clearance for 10 cases twice on the same site. He demonstrated that there was only deviation in average $\pm 1.94\%$ (0.0–5.9%) between the first and the second estimated values and admitted that NaI¹³¹ local clearance was a useful method. In the meantime, average half-time for subcutaneous local clearance estimated by him was 17.0 minutes (K value 0.4076). Lang¹⁸⁾ followed up NaI¹³¹ local clearance at the subcutaneous tissue for 15 cases calculating average half-time to be 26.8 minutes. The author's value was about the mean between Pabst and Lang's values. However, since the injected quantity of NaI¹³¹ and the site of injection and other conditions were not exactly same with theirs, it was hard to compare this figure with the results of their reports.

An average half-time for RISA local clearance was 19.7 hours. This was very close to that of 21.7 hours which the writer obtained from RISA local clearance experienced by dogs.

II. Peripheral Vascular Disease

Raynaud's Disease

For eight patients—one male and seven females—who were hospitalized

TABLE 15. Local Clearance of Raynaud's Disease

Case (No.)	Sex	Age (y. r.)	Half time			
			NaI ¹³¹ (mins.)		RISA (hrs.)	
			R	L	R	L
26	F	24	16.2	14.3	13.5	13.1
27	F	44	13.8	20.2	21.4	18.0
28	F	36	25.0	27.2	18.7	21.0
29	F	21	17.6	29.2	29.7	32.0
30	F	20	23.1	27.3	19.2	17.6
31	F	23	13.8	17.1	21.0	19.4
32	F	34	44.1	30.2	25.1	29.3
33	M	20	38.8	39.1	25.7	17.1
Average			24.1	25.6	21.8	20.9
			24.8		21.4	

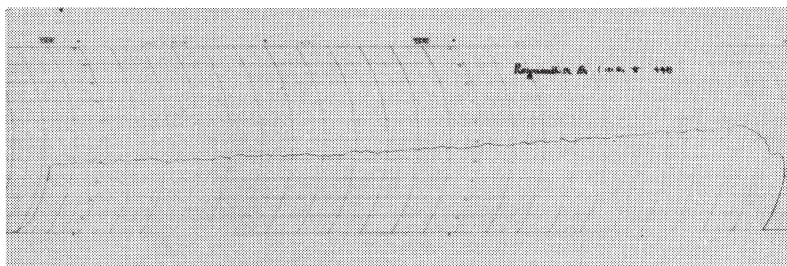
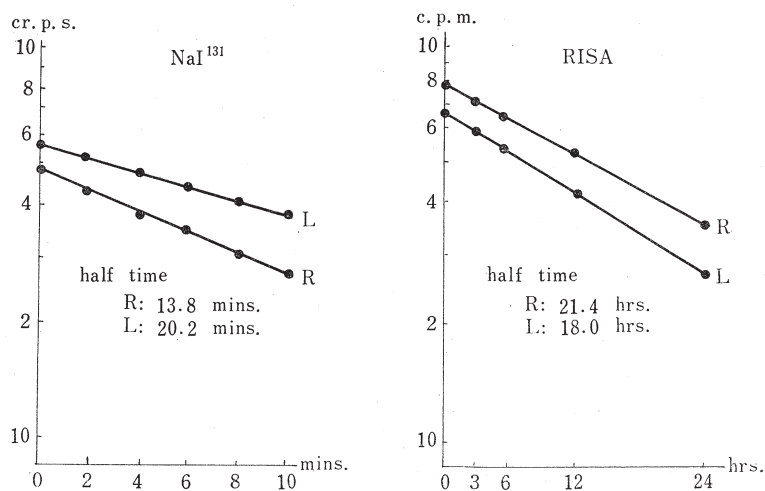
FIG. 23. NaI¹³¹ local clearance curve of Raynaud's disease (case 27 Female 44 ys.)

FIG. 24. Local clearance of Raynaud's disease (case 27 Female 44 ys.)

by clinical consultation, were estimated NaI¹³¹ and RISA local clearances with the result as indicated in Table 15.

Average half-time for NaI¹³¹ local clearance was 24.8 minutes while that for RISA was 21.4 hours. The estimated values of the patients at rest were proved to be no significant difference from those of normal subjects.

Fig. 23 is NaI¹³¹ local clearance for patients having Raynaud's disease recorded in automatic recorder. Fig. 24 is local clearance curves of NaI¹³¹ and RISA for the same patients suffering from Raynaud's disease drawn on half-logarithmic table in contrast to the time.

Buerger's Disease

For eighteen patients who were hospitalised with the clinical diagnosis of Buerger's disease, both NaI¹³¹ and RISA local clearance were followed up with the estimated results as shown in Table 16.

Average half-time for NaI¹³¹ local clearance was 30.3 minutes, but if only the patients were chosen who had necrose on the toes, average half-time was 35.5 minutes, and remarkable retardation could be observed compared with normal subjects. However, further investigation in various cases was carried out and of the eleven patients who had never received the operation of lumbal sympathectomy, average half-time was calculated to be 39.7 minutes. Out of these cases without any operation, half-time being 46.1 minutes only for the patients who had necrose on their toes, was still more intense in their retar-

TABLE 16. Local Clearance of Buerger's Disease

Case (No.)	Sex	Age (y. s)	Half time				Necrosis of toe		Operation	
			NaI ¹³¹ (mins.)		RISA (hrs.)		R	L		
			R	L	R	L				
34	M	30	15.4	14.2	20.0	25.5			L-lumbal sympathectomy	
35	M	41	24.2	49.3	23.6	36.7		+		
36	M	46	23.2	26.8	28.7	25.0				
37	M	24	5.3	8.2	24.1	23.7	+	+	bs-lumbal sympathectomy	
38	M	36	26.2	15.5	17.6	15.8			L-lumbal sympathectomy	
39	M	47	24.6	26.1	25.3	20.2			graft (L-thigh)	
40	M	35	24.2	23.6	27.7	30.2	+	+	R-lumbal sympathectomy	
41	M	34	28.2	26.8	20.0	22.7				
42	M	30	30.0	30.7	22.7	24.0				
43	M	31	53.8	20.4	22.6	19.6	+		R-lumbal sympathectomy	
44	M	34	74.9	40.1	27.5	28.4	+	+		
45	M	34	24.1	43.6	24.9	26.1			bs-lumbal sympathectomy	
46	M	30		40.7		32.9		+	amputation of R-leg	
47	M	28	49.3	40.1	29.2	23.7	+			
48	M	27	36.3	26.2	29.2	26.2	+			
49	M	32	33.1	28.2	27.0	22.6	+			
50	M	42	22.4	26.1	28.2	30.0	+	+	R-lumbal sympathectomy	
51	M	43	44.9	32.7	36.7	30.4	+			
Average			31.8	28.8	25.6	25.8				
			30.3		25.7					
Average of necrotic toe			35.5		28.9					

ation.

Average half-time for RISA local clearance was 25.7 hours whereas that only for the patients who had necrose on their toes was 28.9 hours. Thus RISA local clearance was more retarded than the normal subjects. However, average half-time was 26.9 hours for eleven subjects who had not undergone any operation of lumbal sympathectomy.

Case 44. 34 years old. Male

Chief complaint: Pain on the right leg

Family history: Father died of pneumonia at 64 years old. Mother and brothers healthy.

Personal history: Nothing particular.

History of present illness: Necrosis with pain from 1st to 5th toe started around December 1953, all the right toes were amputated in the hospital April 1954. From around that time the patient felt pain on the left 5th toe. In August 1956 bilateral 2nd, 3rd, 4th lumbal sympathectomy was performed. In October 1960 he complained pain on the left foot twice and on January 7, 1961 he was hospitalized.

Physical Findings: Blood pressure was 148 over 90. The defect of all toes of the right foot was noted. Partial necrosis were noted on the left 1st and 2nd toe. Peripheral arterial pulsation was notable to be felt on A. dorsalis pedis A. tidalis posterior, A. femoralis dextra, A. poplitea dextra while slight pulsation was felt on A. poplitea sinistra.

In arteriography of the left lower extremity, we could recognise thrombosis in A. tibialis anterior and posterior.

For this patient NaI^{131} and RISA local clearances were followed up. Fig. 25 is the record of NaI^{131} local clearance in automatic recorder. Fig. 26 is this patient's NaI^{131} and RISA local clearance curves drawn on half-logarithmic table. Compared with normal subject, inclination was slower.

Arteriosclerosis Obliterance

For six patients—all of them were females—who were hospitalized under the clinical diagnosis of arteriosclerosis, both clearances of NaI^{131} and RISA were followed up and we got the result of estimation as shown in Table 17.

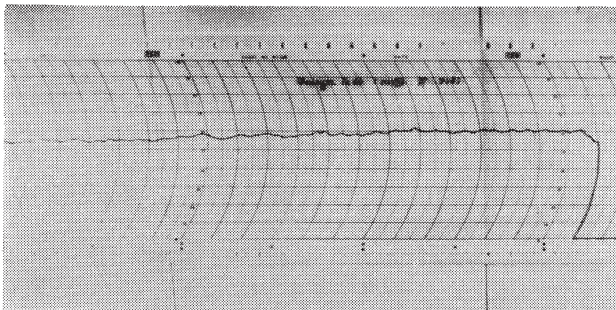


FIG. 25. NaI^{131} local clearance curve of Buerger's disease (case 44 Male 34 ys.)

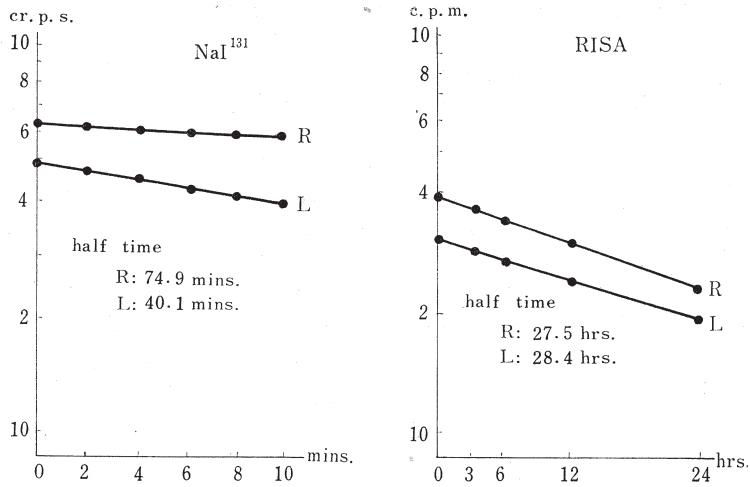


FIG. 26. Local clearance of Buerger's disease (case 44 Male 34 ys.)

TABLE 17. Local Clearance of Arteriosclerosis Obliterance

Name.	Sex	Age (y.s.)	Half time				Blood pressure	Operation
			NaI ¹³¹ (mins.)		RISA (hrs.)			
			R	L	R	L		
52	M	60	∞	43.0	36.9	28.7	138-80 (R)	R-lumbal sympathectomy graft (Aorta)
53	M	57	25.3	32.4	20.0	27.1	140-74 (R)	
54	M	72	∞	∞	37.4	37.3	130-78 (R)	
55	M	59	76.3	44.9	27.8	31.5	148-86 (R)	
56	M	71	27.6	17.0	34.2	36.8	160-100(R)	
57	M	68	58.6	40.2	30.0	42.6	110-70 (R)	
Average					31.1	34.0		
					32.5			

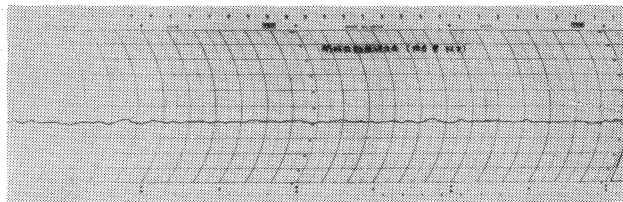


FIG. 27. NaI¹³¹ local clearance curve of Arteriosclerosis Obliterance (case 54 Male 72ys.)

Among them there was no patient suffering from hypertension.

As can be seen from the record in the automatic recorder in Fig. 27, in NaI^{131} local clearance there was some radioactive iodine which was not absorbed at all even 10 minutes later. Comparing with Buerger's disease, half-time for NaI^{131} local clearance was remarkable in the degree of retardation.

RISA local clearance too was 32.5 hours in average half-time retarding than that of Buerger's disease. Fig. 28 is two local clearance curves for NaI^{131} and RISA drawn on half-logarithmic table in contrast to the time; the inclination of the curves was slow as in the case of Buerger's disease. Especially, NaI^{131} local clearance was horizontal with the fundamental line, showing the instance in which NaI^{131} was not absorbed within 10 minutes.

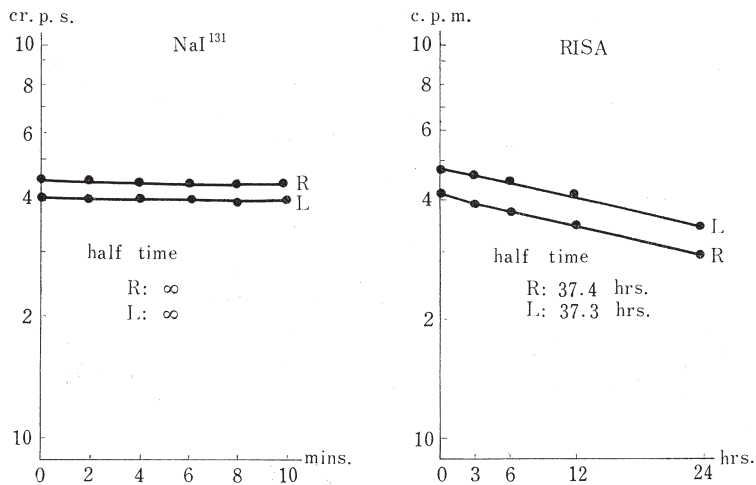


FIG. 28. Local clearance of Arteriosclerosis. Obliterance (case 54 Male 72 ys.)

Venous Thrombosis

For 8 patients—3 male and 5 female—who were hospitalized under the clinical diagnosis of venous thrombosis of lower extremities. Both local clearances of NaI^{131} and RISA were estimated with the results as indicated in Table 18. Their blood pressures were within normal limit and no special case of hypertension was observed.

When the result of estimation for local clearance was divided between the suffered and healthy extremities, average half-time for the former was 42.0 minutes and that for the latter was 28.3 minutes. A remarkable retardation was observed in the suffered extremity. However, it is not of worthy that, even in the healthy extremity, average half-time tends to be in more retardation than normal value.

When average half-time for RISA local clearance was estimated on the suffered and healthy extremities, the average half-time for the former was 16.3 hours, whereas that for the latter was 20.9 hours, showing the suffered

TABLE 18. Local Clearance of Venous Thrombosis

Case (No.)	Sex	Age (y.s.)	Half time				Illed side	Progress
			NaI ¹³¹ (mins.)		RISA (hrs.)			
			R	L	R	L		
58	F	63	26.6	32.4	20.6	13.4	L	acute
59	F	54	14.5	22.0	22.2	20.1	L	acute
60	F	27	38.7	18.9	18.9	12.7	L	acute
61	F	23	22.6	24.3	24.3	12.2	L	acute
62	F	42	31.0	27.5	27.5	21.0	L	chronic
63	M	27	17.7	15.8	15.8	18.6	L	chronic
64	M	42	32.4	17.2	17.2	15.4	L	acute
65	M	28	42.6	21.1	21.1	16.9	L	chronic
Average			28.3	42.0	20.9	16.3		

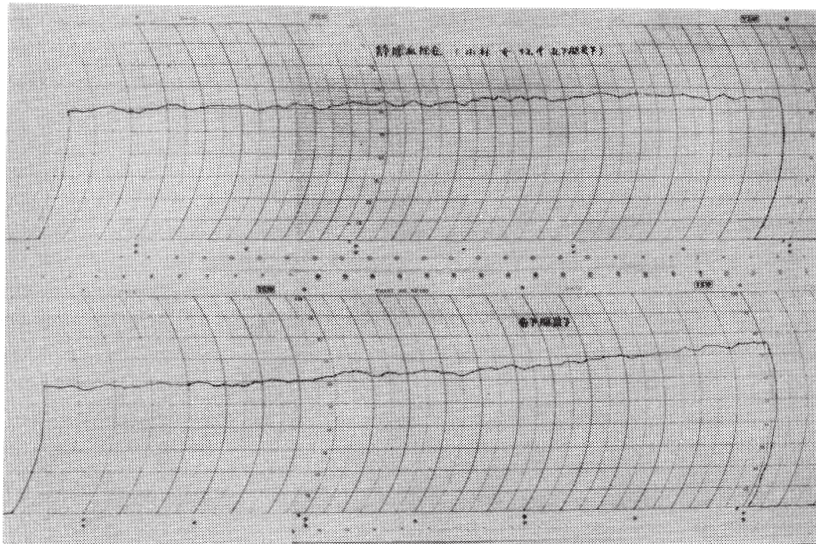
extremity with less retardation. When each case was examined further in detail, extending over all the cases except those who passed through the chronic state, the promotion of RISA local clearance was observed on the suffered extremity.

Case 62. 42 years old. Female

Chief complaint: Swelling of the left lower extremity.

Family history and personal history: Nothing particular.

History of present illness: Six or seven years ago started swelling without any pain on the left lower extremity. From around January 1961, there were redness with pain in the middle of the left lower extremity measuring about 8 cm in diameter, so the patient was hospitalized February 21, 1961.



upper: illed side lower: non-illed side

FIG. 29. NaI¹³¹ local clearance curve of Venous Thrombosis (case 62 Female 42 ys.)

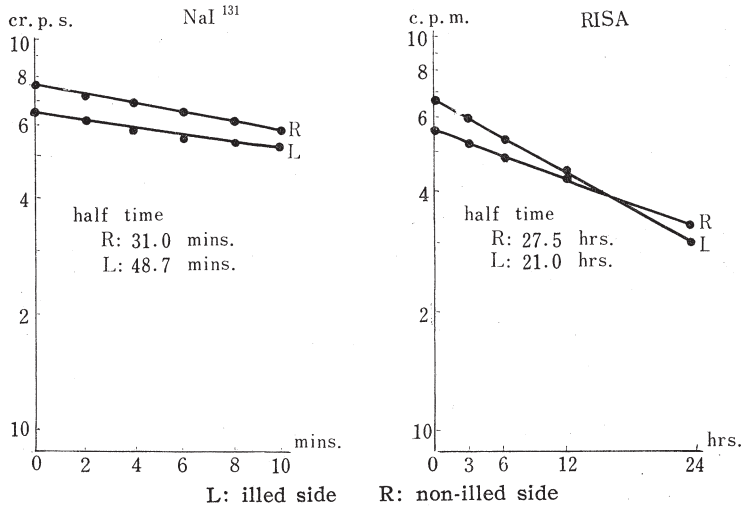


FIG. 30. Local clearance of Venous Thrombosis
(case 62 Female 42 ys.)

Physical findings: Swelling on the left lower extremity. Circumference of the lower extremity was 45 cm right, 49 cm left on the thigh at 15 cm above the knee, right 36 cm left 40 cm on the knee; and right 35 cm, left 41 cm at the middle of the leg. Venography of the left lower extremity showed also obliteration at the middle of v. femoralis dextra. Fig. 29 is the record of this patient's NaI¹³¹ local clearance in automatic recorder.

Fig. 30 is two local clearance curves for NaI¹³¹ and RISA drawn on half-logarithmic table in contrast to the time. As known in this figure, whereas NaI¹³¹ local clearance curve is slow in inclination in the suffered extremity, RISA local clearance curve is sharp in the suffered extremity. We assume this is because blood flow is disturbed in the suffered extremity but lymph flow is stimulated.

Lymphedema (Elephantiasis)

To the cases hospitalized with the clinical diagnosis for lymphatic edema and elephantiasis, both NaI¹³¹ and RISA local clearance were followed up. All these patients were not observed with any dilatation of vein by venography. Table 19 is the result of its estimation.

TABLE 19. Local Clearance of Lymphedema and Elephantiasis

Case (No.)	Sex	Age (y.s.)	Half time				Diagnosis
			NaI ¹³¹ (mins.)		RISA (hrs.)		
			R	L	R	L	
66	M	45	12.1	19.8	∞	36.7	R-traumatic elephantiasis
67	M	56	20.9	12.7	30.7	106.1	L-lymphedema
98	F	22	23.2	26.1	20.5	82.6	L-lymphedema

Average half-time for NaI^{131} is 17.8 hours at the suffered extremity and 21.3 minutes at the healthy extremity, all of these being near to the normal value, whereas in RISA local clearance, a remarkable retardation was observed in the suffered extremity. In one of these cases, almost any RISA was not absorbed within 10 minutes.

Case 66. 45 years old. Male

Chief complaint: Swelling on the right lower extremity.

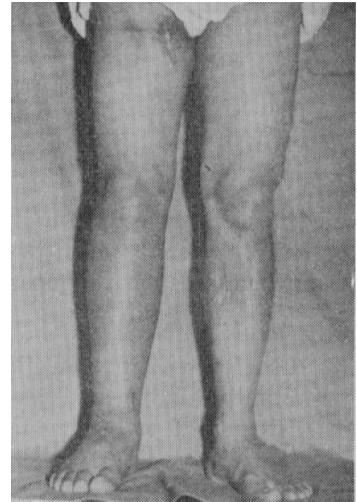
Family history: Parents died of unknown disease, 4 died out of 8 brothers-2 unknown disease, 1 syphilis and 1 peritonitis.

Personal history: He had had lung tuberculosis 20 years ago.

History of present disease: He had gotten shot gun wound on the right thigh 1947, 8 years before had started swelling of the right thigh and he was operated at a local hospital on September 29, 1960.

Physical findings: Right lower extremity was swollen and the skin was extremely thickened. Pulsation of peripheral arteries on both sides could be felt. Dilatation of superficial veins was not remarkable on the left and right side. Circumference of lower extremity was 49.0 cm on right side, 49.0 cm on left side 15 cm above the knee; 37.0 cm, 35.5 cm on the knee and 39.0 cm 35.0 cm at the middle of the leg. As seen in Fig. 31, the wound due to shot gun was seen. Venography showed veins to be within normal limit. This patient's record of NaI^{131} local clearance in the automatic recorder is shown in Fig. 32.

Fig. 33 is NaI^{131} and RISA local clearance curves drawn on the half-logarithmic table. As we can see in these figures, NaI^{131} local clearance tends to be normal or promotive but RISA local



R: illed side

FIG. 31. Traumatic Elephantiasis (case 66 Male 45 ys.)

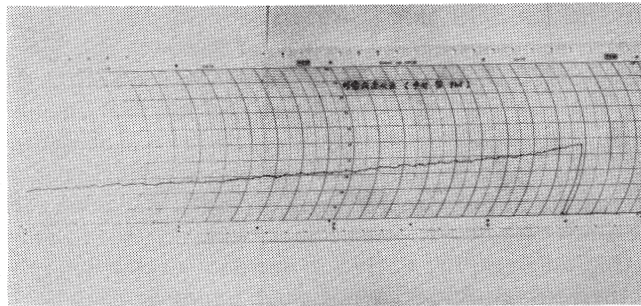


FIG. 32. NaI^{131} local clearance curve of Traumatic Elephantiasis (case 66 Male 45 ys.)

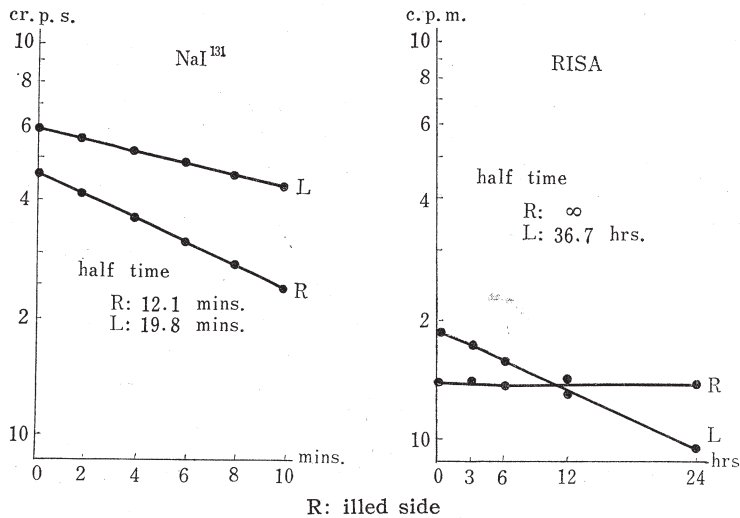


FIG. 33. Local clearance of Traumatic Elephantiasis
(case 66 Male 45 ys.)

clearance is so retarding that almost any absorption was not made in the suffered extremity even in estimated 24 hours. Lymph flow was considerably disturbed and was diagnosed traumatic elephantiasis.

Case 68. 22 years old. Female

Chief complaint: Swelling on the left lower extremity.

Family history and personal history: Nothing particular.

History of present illness: From around 1959 the swelling of the left lower extremity with unknown origin had started followed by the tumor on the left thigh November, 1961. At a local hospital the patient received the operation to extirpate the tumor. Microscopic diagnosis was not obtained at that tissue. Hospitalized June 20, 1962.

Physical Findings: As for peripheral artery, pulsation was palpated on the the lower extremities. However, pulsation on the left extremity was weak, compared with that of right side. Observation in the standing position had not revealed any dilatation of the superficial vein on the lower extremities. The circumference of the lower extremity was measured 47.5 cm on the right side 52.5 cm on the left side 15 cm above knee; 47.5 cm 52.5 cm on the knee and 35.0 cm 39.0 cm at the middle of the lower extremity. Any obliteration was not recognized by venography on the lower extremity. Furthermore, in order to observe the veins up to the bifurcation of v. carva caudalis, venography was taken by inserting catheter v. femoralis dextra. That is shown in Fig. 34. As shown in this venography, v. ilica communis on the opposite side can be seen too, and there is no obliteration caused by thrombosis in the bifurcation of v. carva caudalis.

Fig. 35 indicates the patient's two local clearance curves of NaI¹³¹ and

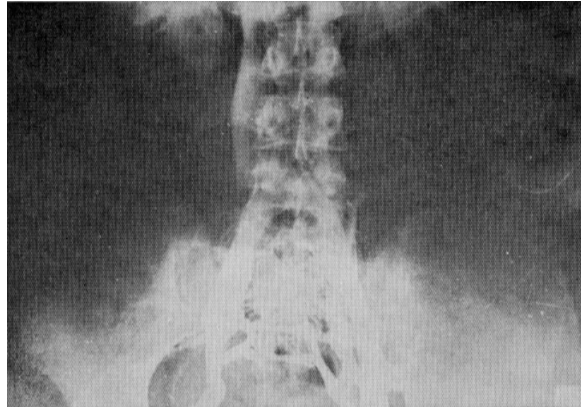


FIG. 34. Venography of V. cava inferior (Lymphedema)
(case 68 Female 22 ys.)

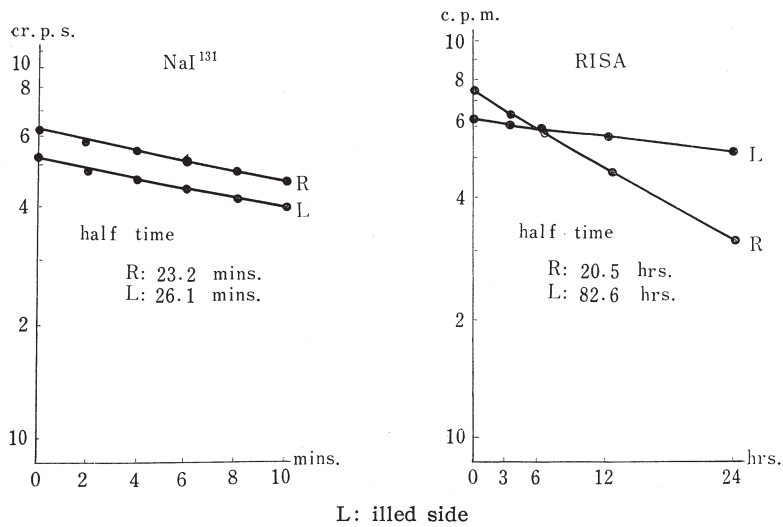


FIG. 35. Local clearance of Lymphedema
(case 68 Female 22 ys.)

RISA. In the case of NaI¹³¹ local clearance curve, there is noticeable variation between the left and right inclination, but RISA local clearance curve is very slow on the suffered extremity, showing the disturbance of lymph flow.

Discussion

In the case of Raynaud's disease, when the patients was at rest, NaI¹³¹ and RISA local clearance measured subcutaneously at the lower extremity fell within the normal range.

In the case of Buerger's disease, arterial obliteration and arteriosclerosis

obliterans, both local clearance of NaI^{131} and RISA were retarded but their retardation were considerable in the cases of Buerger's disease with toe necrosis compared to those without necrosis. The clearance in the case of arterial obliteration was similar with that of experimental dogs induced arterial obliteration.

In the case of arterial obliteration, both blood and lymph flows were disturbed. In venous thrombosis, NaI^{131} local clearance was retarded at the suffered extremity which corresponded well with the reports of Hiei¹⁵⁾ and Rapaport.⁴⁸⁾ On the other hand, RISA local clearance tended to be normal or promotive at the suffered extremity. As ascertained by the experimental dogs induced thrombosis of vein. The NaI^{131} and RISA local clearance indicated that the blood flow was disturbed and the lymph flow was promoted at the suffered extremity.

In the case of lymphedema and elephantiasis, NaI^{131} local clearance was normal or promoted, but RISA local clearance was retarded. Kinmouth⁴⁹⁾ *et al.* injected RISA subcutaneously on the lower extremity of the patients suffering from lymph edema and reported the retarded absorption of RISA by measuring the rate of RISA's disappearance from lower extremity and that appeared in blood.

According to Berg's report too, in the case of arterial obliteration, NaI^{131} and RISA local clearances were retarded, and in the case of thrombophlebitis, NaI^{131} local clearance was retarded and RISA local clearance was promoted, and in elephantiasis, NaI^{131} local clearance was within normal limit and RISA local clearance retarded.

III. Lumbal Sympathectomy

For the vascular diseases such as Raynaud's disease and Buerger's disease, lumbal sympathectomy is common for the treatment. It intends to expand vessels to get the better blood flow. Hitherto, there have been various studies to examine the blood flow of the patients before and after receiving lumbal sympathectomy by measuring the dermic temperature, sweating test, plethysmography, and NaI^{131} local clearance in order to ascertain the result of operation.

However, investigations about lymph flow have been neglected. In order to study the latter points, was measured both NaI^{131} and RISA local clearances of the patients comparing the conditions before and after their lumbal sympathectomy.

The Result

For 2 patients (all female) suffering from Raynaud's disease and 3 patients (all male) of Buerger's disease who were all operated with lumbal sympathectomy, both NaI^{131} and RISA local clearance were measured before and after the operation. All counts were effected from one week to one month after the operation.

The result is shown in Table 20. Average half time for NaI^{131} local clearance is 27.0 minutes before the operation, showing the increase in blood

TABLE 20. Local Clearance of Lumbal Spmpathectomy

Case (No.)	Sex	Age (y.s.)	Diagnosis	Half time								Ope. side	Measured day after ope.
				Before operation				After operation					
				NaI ¹³¹ (mins.)		RISA (hrs.)		NaI ¹³¹ (mins.)		RISA (hrs.)			
R	L	R	L	R	L	R	L						
51	M	43	Buerger's disease	44.9	32.7	36.7	30.4	22.8	30.6	32.7	30.7	R	30
50	M	42	Buerger's disease	22.4	26.1	28.2	30.0	20.4	22.9	28.8	27.2	R	11
42	M	30	Buerger's disease	30.0	30.7	22.7	24.0	22.5	27.9	23.9	25.1	bs	10
31	F	23	Raynaud's disease	13.8	17.1	21.0	19.4	12.2	10.0	24.9	23.5	bs	20
28	F	36	Raynaud's disease	25.0	27.2	18.7	21.0	18.2	14.5	20.3	18.3	bs	14
Average				27.2	26.8	25.5	25.0	19.2	21.2	26.1	25.0		
				27.0		25.2		20.2		25.5			

Ope. side: operated side

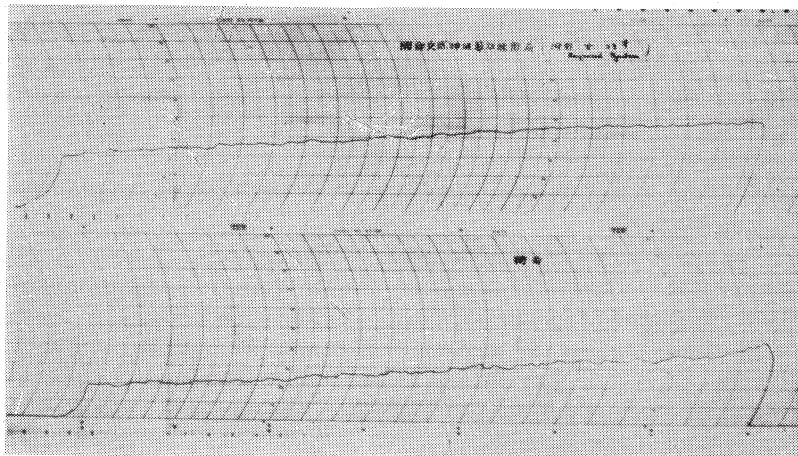
flow as a result of operation. Almost any influence of operation over the lymph flow has not been observed.

Case 31. 30 years old. Female

Chief complaint: Coldness and pain on the both feet.

History of present illness: Pulsation of peripheral arteries was felt on both legs. Both legs were slightly discoloured. Any dilatation of vein or thickened skin was not observed on both legs.

In May, 1961 bilateral 2nd and 3rd lumbal sympathectomy was done and 20 days after NaI¹³¹ and RISA local clearances were measured. Fig. 36 is the pre and post operative record of NaI¹³¹ local clearance by the automatic recorder. Fig. 37 is NaI¹³¹ and RISA local clearance curves. After the opera-



upper: before Lumbal Sympathectomy
lower: after Lumbal Sympathectomy

FIG. 36. NaI¹³¹ local clearance curve of Lumbal Sympathectomy (case 31 Female 23 ys. Raynaud's disease)

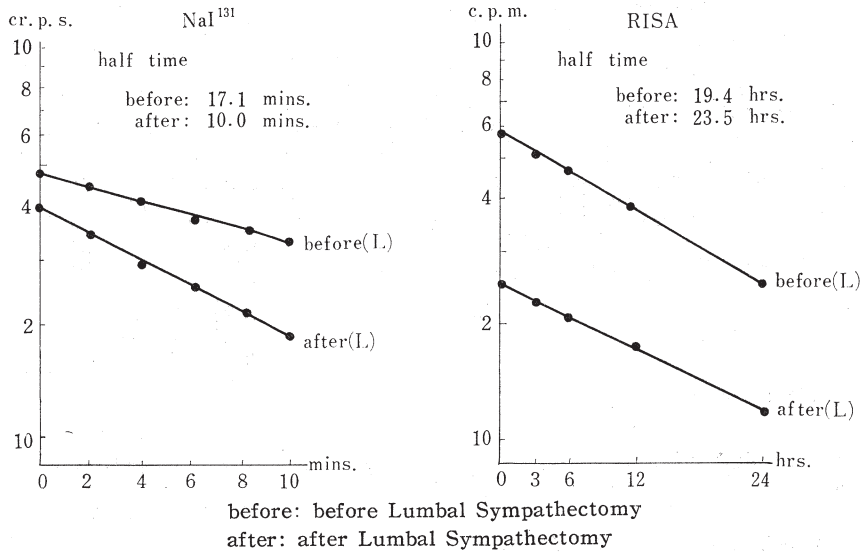


FIG. 37. Local clearance of Lumbal Sympathectomy
(Case 31 Female 23 ys. Raynaud's disease)

tion NaI^{131} local clearance curve showed rapid inclination indicating the increase of the blood flow, but RISA local clearance curve did not vary before and after the operation indicating that lymph flow was not influenced by this operation.

Discussion

As to what influence lumbal sympathectomy gives to the blood flow on the legs was measured by Hiei¹⁴⁾ with NaI^{131} local clearance at gastrocnemius and the skin covering it, and he reported that after the operation the local clearance retarded at gastrocnemius, but was promoted on the skin covering gastrocnemius. Rapaport⁴⁸⁾ followed up the local clearance with both NaI^{131} and Na^{24}Cl explaining that, if sympathetic block was done, the local clearance on gastrocnemius was retarded, but these of subcutaneous space over gastrocnemius was promoted.

As to autonomic nerve system over lymph vessels, there are still many unclarified points. Camus⁵⁰⁾ admitted the dilatation of the thoracic duct by stimulation of thoracic sympathectomy. Saito⁵¹⁾ reported the ascension of pressure of thoracic duct by stimulating cervical sympathectomy. Hatta⁵²⁾ reported that the lymph flow in the thoracic duct decreased by stimulation of cervical and thoracic sympathetic nerves. Nishimaru⁵³⁾ admitted that the dog's lymph duct along v. saphena parva was shrunked by the stimulation of lumbal N. sympathicus: ductus chyli shrunked with the stimulation of N. vagus and cisterna chyli with N. splanchnicus major. However, there are some points with which these reports do not agree. There are very few reports on the variation in lymph flow by the block in autonomic nerves. There is

only one report by Haynes⁵⁴⁾ who explained that although dermic temperature ascended by amputation of these nerves followed by active hyperemia, and there was also change of lymph flow. However, this report corresponded with the result of NaI¹³¹ and RISA local clearance after lumbal sympathectomy.

We may conclude that, in lumbal sympathectomy, the blood circulation in the leg increased but only little influence of lymph flow was noted.

IV. Adrenomedullectomy

Adrenomedullectomy was administered first on human being by Constantini in 1927 and by Leriche⁵⁵⁾ and Stricker. Around 20 years ago Durante⁵⁵⁾ operated patients having adreno medullar hyperfunction such as Raynaud's disease, endo-arteritis obliterans (juvenil and senile), Hypertension (essential and malignant), scleroderma, etc. However, as the origin of these diseases has not been clarified, adreno medullectomy was done as a symptomatic treatment. There are still many points unclarified in adrenomedullectomy. In Japan, Kuwabara⁵⁵⁾, Hashimoto and Kamiya⁵⁷⁾ *et al.* did this operation in the cases of Buerger's disease.

The Result

For 5 cases (all men) of Buerger's disease both NaI¹³¹ and RISA local clearance were estimated before and after adrenomedullectomy. Post operative estimations were effected from one week to one month.

The result of estimation is shown in Table 21. Average half-time for NaI¹³¹ local clearance was 39.4 minutes before the operation and 39.0 minutes after the operation; no significant difference was recognized between the two.

Average half-time for RISA local clearance was 27.7 hours before the operation and 27.1 hours after the operation showing no significant difference between before and after.

However, according to Iwase⁵⁷⁾ the estimation of adrenaline in urine is shown in Fig. 38. It is demonstrated that the adrenaline materials reduced in blood by adrenomedullectomy.

TABLE 21. Local Clearance of Adrenomedullectomy (Buerger's disease)

Case (No.)	Sex	Age (y.s.)	Half time								Ope. side	Measured day after ope.	Operation
			Before operation				After operation						
			NaI ¹³¹ (mins.)		RISA (hrs.)		NaI ¹³¹ (mins.)		RISA (hrs.)				
R	L	R	L	R	L	R	L						
44	M	34	74.9	40.1	27.5	28.4	69.6	47.8	28.6	27.9	L	8	amputation of R-leg
46	M	30		40.7		32.9		44.3		30.7	L	29	
47	M	28	49.3	40.1	29.2	28.7	38.6	42.3	28.3	26.0	bs	18	
49	M	32	33.1	28.2	27.0	22.6	33.8	30.3	26.8	20.4	bs	30	
50	M	42	22.4	26.1	28.2	30.0	20.0	24.8	27.5	28.1	bs	9	
Average			44.9	35.0	28.0	27.5	40.5	37.8	27.8	26.6			
			39.4		27.7		39.0		27.1				

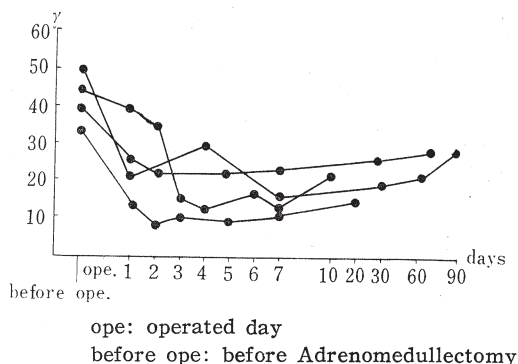


FIG. 38. Adrenalin in urine (Adrenomedullectomy)

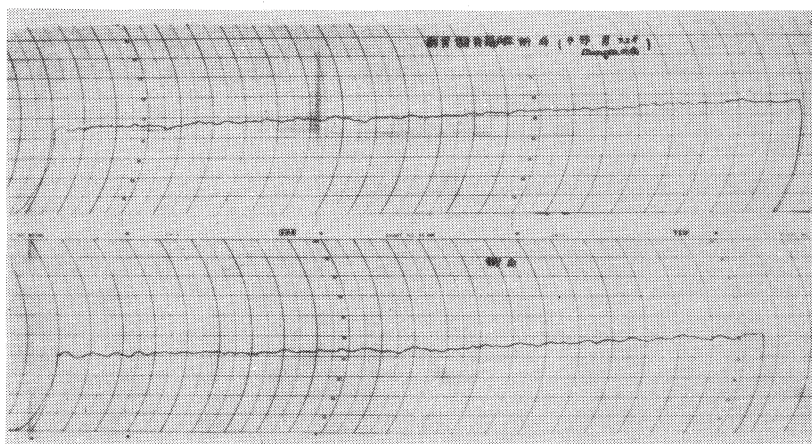
Case 49. 32 years old. Male

Chief complaint: Ulcer of right foot.

Personal history: Nothing particular.

Family history: Father died of angina pectoris.

History of present illness: In 1953 he had complained coldness and pain on the left leg. In 1958, because of ulcer formation on 1st and 2nd toe of left foot, he had been hospitalized in a local hospital and had been operated with the amputation of 1st and 2nd toe of the left foot as well as left lumbar sympathectomy and periarterial sympathectomy of A. femoralis sinistra. In April 1960 because of ulcer on right foot he had received 2nd, 3rd, and 4th right lumbar sympathectomy in our department. After the operation, he had not felt any cold and pain on the suffered foot, but size of ulcer had not reduced. From around



upper: before Adrenomedullectomy
lower: after Adrenomedullectomy

FIG. 39. NaI^{131} local clearance curve of Adrenomedullectomy
(Case 49 Male 32 ys. Buerger's disease)

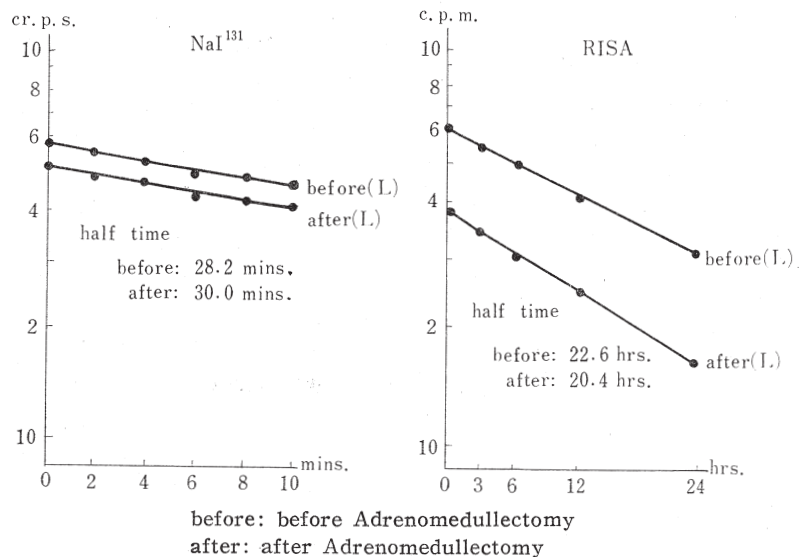


FIG. 40. Local clearance of Adrenomedullectomy
(Case 49 Male 32 ys. Burger's disease)

February 1961, ulcer on the right foot had started to grow, so he was re-hospitalized July 6, 1961.

Physical Findings: Blood pressure was 110 over 78 (mm/Hg). As for peripheral arteries, pulsation could not be felt on both sides of A. poplita, A. tibia posterior and A. pedis dorsalis. 1st and 2nd toes of left foot were amputated at the base.

July 15, 1961 he was operated bilateral adrenomedullectomy. Fig. 39 is the pre and post operative record of NaI¹³¹ local clearance in the automatic recorder. Fig. 40 is same patient's NaI¹³¹ and RISA local clearance curve. In this case no significant difference was noted before and after the operation.

Discussion

It has been known that peripheral vessels shrink with adrenaline materials. There is no definite thought about such pharmaceutical effect on lymphatic vessels. Pullinger⁵⁸⁾ reported that, although lymph trunks of rats and pigs shrink with adrenaline, pituitrin, the lymphatic vessel of rats ear did not shrink with the administration of one or all of these drugs. Hatta⁵²⁾ also admitted that the thoracic duct shrank with adrenaline. Steggerd⁵⁹⁾ connected a dog's thoracic duct and cervical vein with polyethylene tube, and tried to observe lymph flow in physiological state as possible. He reported that intravenous injection of epinephrin or non epinephrin alone stimulated lymph flow. However, its mechanism was still unknown.

By the author's RISA and NaI¹³¹ local clearance even in the cases where adrenaline decreased in urine by adrenomedullectomy was not shown any significant difference before and after the operation. On the other hand,

there is the report⁶⁰⁾ that NaI^{131} local clearance is retarded by adrenaline injection. The reason why there is no significant difference in both local clearances of NaI^{131} and RISA before and after the operation is ascribed as follow: (I) The decrease in catechol amine is not enough to give the change in this estimate. (II) In most of Buerger's disease in which the main arteries are blocked, the effect of operation does not appear in this test. (III) Actually, as there is no significant difference in both local clearance before and after the operation, the blood and lymph flow does not change before and after the operation.

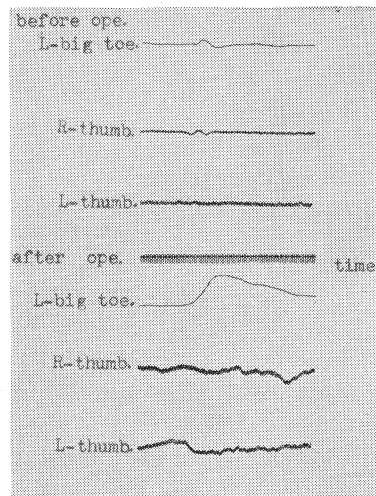
At any rate the action and mechanism of adrenomodullectomy depend on the studies in the future, since there are still many unclarified points in them.

Meanwhile, Kuwabara⁶¹⁾ *et al.* did adrenomodullectomy for the patients having Buerger's disease and reported that NaI^{131} local clearance tended to be promoted after the operation. This contradicts with the writer's result of estimation. However, as may be known from Fig. 41, the result of reflex photoelectric plethysmograph (r.p.p.) applied to the patients who were operated adrenomodullectomy for Buerger's disease, did not show much difference before and after the operation. This corresponds well with the result of writer's NaI^{131} local clearance, so we assume that before and after adrenomodullectomy no significant difference in NaI^{131} local clearance was noted.

Comments

In the basic experiments of RISA local clearance by dogs, was ascertained that RISA was mainly observed by the lymph flow. This coincided well with report of Field *et al.*⁶²⁾ that, when horse's serum was injected subcutaneously, almost all of it was absorbed through lymphatic vessels. Yoffey⁶³⁾ *et al.* reported that, in nasal mucosa serum albumin in the size of molecules would be absorbed from the lymphatic vessel. Ruzzuyak⁶⁴⁾ explained that almost all colloid with more than 20 000 molecular weight could be absorbed from lymphatic vessels. If we consider that molecular weight of RISA is 67 800, RISA may be absorbed only through lymph vessels

On the other hand, according to the biological microscopic observations by Zweichfach⁶⁵⁾⁶⁶⁾⁶⁷⁾ Landis⁶⁸⁾ *et al.*, red cells as well as materials sized more or less of red cells passed through capillary walls. There is a critics in this report that the capillary wall was not in physiological state and also this does not



before ope: before Adrenomedullectomy
after ope: after Adrenomedullectomy

FIG. 41. Reflex photoelectric plethysmograph of Adrenomedullectomy (Case 69 Male 38 ys. Buerger's disease)

explain the site of pass from tissue into lymphatic vessels.

In the experiments of NaI^{131} local clearance by dogs, most of NaI^{131} was absorbed from the blood flow, but the lymph flow did not play any significant role. This is same with Stone's report. Thereupon, was utilized NaI^{131} local clearance as the means to measure the blood flow in the local tissue. As a means of measuring lymph flow through the local tissue, was applied RISA local clearance.

At rest, the patients of Raynaud's disease showed no significant difference from normal persons in both local clearances of NaI^{131} and RISA, and the patients' blood and lymph flow were not disturbed as well.

In Buerger's disease and arteriosclerosis obliterans, both local clearances of NaI^{131} and RISA were retarded, which coincided well with both local clearances by experiments of dogs induced arterial thrombosis. As mentioned before, and as known by Irisama's⁴⁷⁾ report on the experiment with frogs, we assumed that arterial congestion disturbed not only blood flow but also lymph flows.

The result of both local clearances of NaI^{131} and RISA of patients having thrombosis of veins corresponds with that of animal experiments of dogs, namely, NaI^{131} local clearance was retarded on the suffered extremity on which, however, was promoted RISA local clearance. These endorsed the fact that blood flow was disturbed and lymph flow was stimulated on the suffered extremities.

Here is the question of permeability through capillary wall in case of venous congestion. According to Landis's⁶⁹⁾ report, under venal pressure at 80 mmHg, protein in transdated fluid was 1.5% in average and at 60 mmHg less than 0.3% in average. Meanwhile, the result of measuring protein contents in edema fluid collected from the patients suffering from venous congestion had revealed that the protein contents did not exceed 0.39-0.09%. By this he affirmed that capillary wall would not transdated 95% of plasma protein. In case of normal persons, capillary pressure in the arteriolar loop was 430 mm H_2O and in the venous loop 160 mm H_2O .⁷⁰⁾ However, considering that, from the writer's experiments of dogs induced venous thrombosis, those whihc were clearly caused with edema were counted the pressure of saphenous vein to be 283 mm H_2O in average, he assumed that even in the case of venous congestion almost any RISA would not be transdated through capillary wall. Pullinger⁶⁸⁾ Gergly⁷¹⁾ observed that whereas at the part showing edema, blood vessels were either in oppressed or shrinked state, and then lymphatic capillary vessels were expanded. Lymphangiography of experimental dogs induced venous thrombosis had enabled to observe this fact very well. McMaster⁷²⁾ *et al.* recognized the promoted permeation at the part with edema and Cameron⁷³⁾ *et al.* reported that, in case of pulumony edema induced by phosgen lymph flow in lung increased rapidly. In such venous thrombosis, it was assumed that tissues became edematous to make tissue pressure ascend, capillary lymphatic vessel expanded for the increased lymph flow.

In the case of lymph edema and elephantiasis, like that of experimental dogs induced lymph edema, NaI^{131} local clearance was normal at the suffered

extremity, while RISA local clearance was noticeably delayed causing much disturbance of the lymph flow.

To the patients having peripheral vascular disturbance, lumbal sympathectomy and adrenomedullectomy has been applied, however, no report has been made on the change in lymph flow of the patients after one of these operations. The writer measured NaI^{131} and RISA local clearance of patients immediately before and after the operations to examine what kind of influence the operation might give on the peripheral blood flow and lymph flow. In case of the patients operated lumbal sympathectomy, NaI^{131} local clearance was found to promote after the operation, while RISA local clearance indicated no significant difference before and after the operation. As for nerve governing thoracic duct and chyli duct there are reports by Camus,⁵⁰⁾ Saito,⁵¹⁾ Hatta,⁵²⁾ Nishimaru⁵³⁾ *et al.* Their theories are not definite leaving many unclarified points. Few works were only reported about the nerves governing peripheral lymphatic vessels. Nishimaru⁵³⁾ reported that lymphatic vessel along v. saphena parva, shrank with the stimulation of lumbal sympathetic nerves. As for the change in lymph flow at the time of the block in autonomous nerves, we have only Hayne's⁵⁴⁾ report that the blood circulation increases, while there is either no change in lymph flow or so slight in any, which cannot be caught with this method.

As the result of NaI^{131} and RISA local clearance of the patients, there was no significant difference before and after adrenomedullectomy. Kuwabara⁶¹⁾ *et al.* reported that NaI^{131} local clearance was often promoted after the operation which did not go along with the writer's experiment. However, according to the result of R.P.P., we assume that there is no significant difference in NaI^{131} local clearance before and after operations. There are many unclarified points as to the mechanism of adrenomedullectomy. Further investigations have to be made in these points in future. At least in the case of Buerger's disease operated adrenomedullectomy, there was no definite change in the blood and lymph which could be detected between the estimated values obtained before and after the operation.

CONCLUSION

Applying NaI^{131} and RISA local clearance, we have studied peripheral flows by comparing vascular system with lymphatic system, and found these method to be excellent through all managements upon clinical as well as experimental works. Two local clearances were administered to the cases of peripheral disturbance or those received lumbal sympathectomy and adrenomedullectomy, and the followings had been obtained:

All were estimated subcutaneous space of the lower extremity.

- (1) There was no difference between the local clearance of radioactive iodine (I^{131}) and that of radioactive sodium (Na^{24}).
- (2) RISA local clearance mostly concerned with the lymph flow.
- (3) There was definite change of local clearance in the case of Raynaud's disease.

(4) In case of arterial obliteration (Buerger's disease, arteriosclerosis obliterance), both blood and lymph flows were disturbed similarly to experimental arterial thrombosis.

(5) In venous thrombosis the blood flow on the suffered extremity was retarded, but the lymph flow was promoted compensatively, as in the case of experimental dogs induced thrombosis of the veins.

(6) In the case of lymphedema and elephantiasis as in the experimental case, the lymph flow was disturbed at the suffered extremity.

(7) In lumbal sympathectomy, compared with the state prior to the operation, the blood flow was promoted but no significant change in the lymph flow after the operation.

(8) In adrenomedullectomy, there was no significant change in the blood and lymph flows on the leg before and after the operation.

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