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Experimental Studies on Lymphatic Drainage of the Peritoneal Cavity Using ^{198}Au-Colloid*

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Summary

The lymphatic drainage from the peritoneal cavity was studied scintigraphically and by determination of the specific accumulation of ^{198}Au-colloid and of the ^{198}Au-contents within the regional lymphatics, liver and spleen following intraperitoneal injection of 25 µCi in 29 rabbits. The investigation revealed the selective ^{198}Au-accumulation in the mediastinal lymph nodes and within the lymphatics of the greater omentum, whose absorptive capacity was shown to be significant. The theoretical background for visualization of the mediastinal lymph nodes scintigraphically and for the transposition of the greater omentum in the treatment of lymphedema was explained by these results. Moreover, it was previously suggested, that intraperitoneal radiotherapy affects the regional lymphatic system of the peritoneal cavity as well. The lack of radioactivity in the mesenteric lymph nodes and in the thymus indicated, that these organs do not participate in the lymphatic drainage mechanism of the peritoneal cavity.

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Intraperitoneal absorption into lymphatics takes place primarily at the peritoneal surface of the diaphragm. According to *von Recklinghausen's* fundamental observation (24) this route, i.e. through the thorax to the anterior mediastinal lymph nodes was confirmed by using proteins, inactive particles, cellular elements (2, 7, 7, 29) and especially by roentgen contrast media (9, 15, 19, 22). *Sahavedan*(25), *Anghileri* (4), *Atkins* et al. (5) and *Langhammer and Eisenburg* (17) reported on the use of radioactive colloids for exploring the lymphatic drainage of the peritoneal cavity. Accumulation of ^{198}Au-colloid within the mediastinum was first documented by *Müller* (1956), who used the intraperitoneal application for therapeutic purposes. Other papers concerning experimental studies and human autopsies only ruled out, that an effective radiation therapy includes the radiation of the serosal surface as well as the regional drainage areas because of a "paraselective" accumulation of radioactivity (1, 3, 10, 12, 14, 23). Systematic researches for the regional lymphatic system of the peritoneal cavity were not carried out by these authors. Now, in order to explore the distribution and pattern of ^{198}Au-colloid applied in tracer doses, an exact quantitive determination of accumulated radiocolloid in the regional lymphatic system in comparison to the other organs is necessary. To do this we decided for an animal experiment on rabbits.

Some years ago we demonstrated the possibility of visualizing lymph nodes in the mediastinum by the intrapleural application of the above radiopharmaceutical (16).

Method

25 μCi of ^{198}Au microcolloid (standardized by a dose calibrator) with a range up to 150 Å together with 75 units of hyaluronidase (Kinetin®) were injected into the peritoneal cavity of 29 anaesthesized grown up rabbits of an average weight of 3 kg. Scanning of the whole animal was started 24 hrs post injection using a conventional scanner (Scintimat II, Fa. Siemens).

Immediately after scanning, the rabbits were sacrificed. All the lymph nodes of the mediastinum were dissected and the radiogold accumulation (= radioactivity) of each node determined individually by means of a well counter. The same was done with the greater omentum and liver, spleen, kidney, adrenal, ovary, thymus, lung, heart, thyroid. In the first series of 12 rabbits only the specific accumulation of ^{198}Au (cpm/mg) was determined. In a second series of 17 rabbits, the concentration of radioactivity (in terms of cpm/mg organ weight) was additionally determined and expressed as a percentage of the amount of the injected dose.

For an exact statistical evaluation the significance of the differences of the specific ^{198}Au-accumulation between the liver on the one hand and the spleen or the other organs investigated on the other hand had to be determined. This having been done we applied the procedure of paired differences and the Student's test of significance.

Results

Twentyfour hours after intraperitoneal application of ^{198}Au-colloid complete resorption and selective accumulation of the radiopharmaceutical was observed in the regional lymphatics scintigraphically as shown in Fig. 1. As a rule we found focal hot spots in the region of the superior thoracic aperture and a stripe of radioactivity along the curvature major ventriculi indicating the greater omentum.

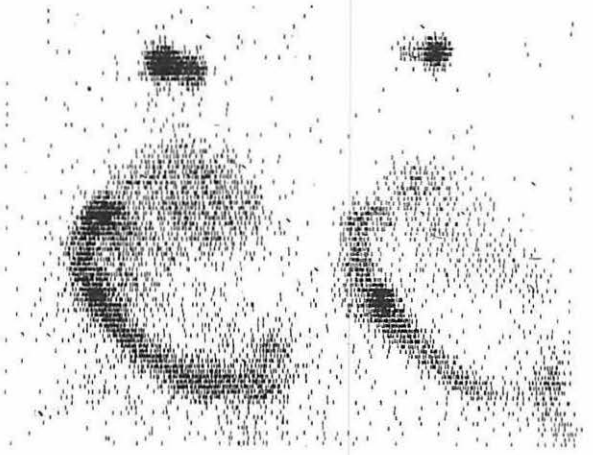

Fig. 1. Whole body scans of two rabbits showing the distribution of radioactivity 24 hrs after intraperitoneal injection of 25 μCi ^{198}Au-colloid

Locational differences in the radioactivity accumulation within the mediastinum of the right and left side are due to the remarkable variations in the topographic configuration and distribution of these mediastinal lymph nodes (Fig. 2). These scintigraphical findings were documented in accordance with the results, obtained by preparation of all mediastinal lymph nodes (Table 1). Besides the variation of the number of lymph nodes, the weight of each single node ranged between 0,5 mg and 114 mg. In in-vitro-measurements all mediastinal lymph nodes as well as tissue samples of the greater omentum regularly showed significantly higher uptake rates of radiocolloid when compared to those of all other organs investigated. But definite quantitative differences, in radioactivity levels (expressed as a percentage of the injected dose per lymph node) were established for each lymph node excised from the mediastinum (Table 2). The extent of accumulation of radioactivity was not proportional to the weight of the single lymph node in any rabbit, i.e. the differences in radioactivity contents ranged from 0,001% to 16,94%. Similarly the total amount of concentrated ^{198}Au-colloid of all lymph nodes within the mediastinum of each rabbit varied between 5,93% and 31,46% of the injected radioactivity.

As can be seen from Table 3, particularly high values of specific accumulation (cpm/mg) were registered in tissue samples of the greater omentum. The total amount of each of the 17 animals fluctuated between 5% to 25% of the intraperitoneally injected radioactivity, if the extremes at both ends are omitted.

In comparison with other organs, liver and spleen (Table 4) showed slight, but constantly higher values of specific ^{198}Au-accumulation. These were found to be of the same magnitude. That is to say that there is no statistically significant difference in the specific accumulation of ^{198}Au in these organs. Due to the different organ weights, however, the total radioactivity level of the liver amounted to a maximum of 53,8% and of the spleen to 1,04% of the injected dose.

Finally we observed significant differences in the specific radioactivity (cpm/mg) of liver in comparison with the mesenteric lymph nodes and the other organs, with exception of the pancreas (Table 5). This statistical result suggests, that the latter values of specific ^{198}Au-accumulation correspond to background rates, indicating no increased accumulation of ^{198}Au-colloid within the lymph nodes of the root of the mesentery, kidney, adrenal, heart, thymus and thyroid.

Table 1. Number and weight (mg) of mediastinal lymph nodes (17 rabbits)

Animal No.	number of single nodules										
	1	2	3	4	5	6	7	8	9	10	11
1	33	15	21	29	72	43	59	4			
2	49	29	9								
3	15	8	28	78	77	10					
4	16	44	6	43	60						
5	6	28	6	10	103	7					
6	24	55	112	114	96	34	–				
7	23	17	10	65	34	50	14				
8	36	28	0,5	2	7						
9	8	3	3	9	9	63	98				
10	11,5	3	14,5	2,5	2,7	2	3	1,5	27	37	87
11	4,5	9,5	8	6	2,5	4	2	3,5	8		
12	24	22,5	31	29	6	2	1,5	3			
13	48	48	2	2	2	49,5					
14	12	14	43	24	4	3,5	1,6	4			
15	47	22	6	1,5							
16	35	25									
17	9	9	17	2	4	5	2				

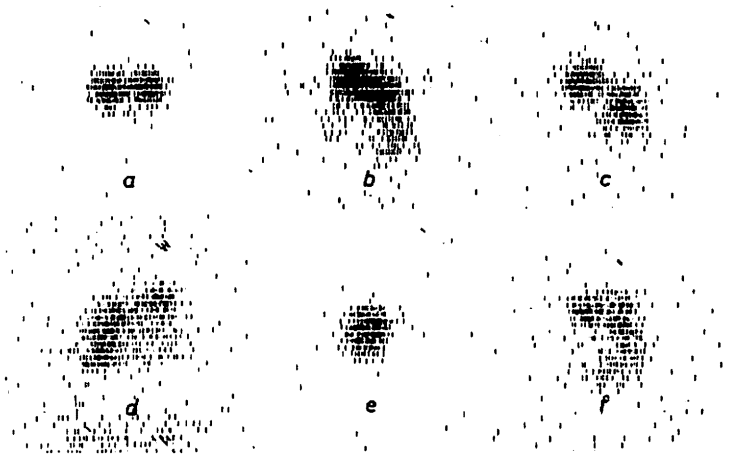

Fig. 2. Mediastinal scans of 6 rabbits 24 hrs following intraperitoneal application of 25 μCi ^{198}Au-colloid

Discussion

In accordance with previous papers (4, 5, 16, 25) we succeeded in confirming the selective accumulation of radiogold colloid in the mediastinum scintigraphically, while at present no appropriate contrast material is available for an analogous X-ray procedure (*Koehler and Rodriguez* 1968). By in-vitro-measurements this uptake of ^{198}Au has been found only in the lymph nodes. In contrast to the findings of *Anghileri* (4) no radioactivity was, however, observed in the thymus. The lack of ^{198}Au-accumulation within the thymus enhances the assumption that this organ does neither participate in the upper thoracic lymph flow, nor does it accumulate ^{198}Au-colloid from the blood stream. A similar behaviour was seen in the mesenteric lymph nodes, which do not join the lymphatic drainage system of the peritoneal cavity.

Table 2. ^{198}Au-colloid uptake of the single lymph nodes and of total mediastinal lymph nodes of 17 rabbits 24 hrs following intraperitoneal injection of 25 μCi (in terms of percentual relation)

Animal No.	number of single lymph nodes											% uptake of ^{198}Au-colloid in all mediastinal lymph nodes
1	1	2	3	4	5	6	7	8	9	10	11	
1	9,93	0,51	5,86	0,09	0,9	0,11	0,25	0,88				18,53
2	5,58	6,47	0,48									12,53
3	3,95	1,10	2,65	0,26	0,25	0,01						8,22
4	16,94	12,20	0,11	1,01	1,2							31,46
5	2,37	0,27	1,01	1,35	0,001	0,025						5,93
6	5,27	5,23	1,15	1,85	0,82	0,025						14,35
7	4,3	1,83	2,69	2,04	0,53	1,03	0,24					12,66
8	2,51	3,71	0,23	0,37	0,61							7,43
9	1,01	0,86	0,34	1,04	0,02	1,78	0,75					6,80
10	3,01	0,6	2,83	0,5	0,13	0,56	0,54	0,12	0,75	0,68	2,26	11,98
11	0,79	3,2	7,1	0,02	1,03	1,07	0,59	0,41	0,34			14,55
12	0,23	0,064	2,19	4,58	0,09	0,05	0,004	0,008				7,22
13	6,7	6,7	0,01	1,45	0,014	0,067						14,94
14	1,95	1,68	2,79	3,26	0,07	0,07	0,16	0,03	0,18			10,19
15	4,84	8,68	0,55	0,13								14,20
16	5,23	3,95										9,18
17	3,44	3,36	3,89	0,31	0,56	4,8	0,63					16,99

Table 3. Specific accumulation of radiogold (cpm/mg) and radioactivity contents of the total omentum majus, expressed in % of injected dose (n = 17 rabbits)

Animal No.	Specific accumulation of radioactivity (cpm/mg) of tissue samples					total weight	radioactivity contents+
	left		middle	right			
1	797	992	2244	1154	1137	2,5	47,6
2	31	123	46	55	–	5,6	5,52
3	13	49	516	426	293	3,3	6,3
4	361	85	239	201	125	5,36	14,69
5	37	500	214	167	404	3,5	13,5
6	32	279	544	393	–	2,27	10,19
7	51	61	448	299	117	6,8	19,70
8	0,5	1,4	5,9	6,7	1,5	60	2,17
9	5,4	15	11	95	5	17,1	6,0
10	11	9	270	27	17	33,5	16
11	6,1	2,5	18	30	5,8	14	2,38
12	17	35	–	688	100	5,06	9,6
13	93	18	423	1123	429	6,22	25,4
14	45	83	226	118	87	7,2	9,3
15	26	2,1	192	124	23	11,2	9,4
16	9	135	20	4	156	9,7	8,65
17	19	3	193	66	33	9	8,73

+% injected dose related to the total weight of the greater omentum

Table 4. Specific accumulation of radioactivity (cpm/mg) and radioactivity contents of total liver and spleen expressed in % of injected ^{198}Au 24 hours p.i. (n = 17 rabbits)

Animal No.	liver			spleen		
	cpm/mg	weight (g)	% of injected ^{198}Au	cpm/mg	weight (g)	% of injected ^{198}Au
1	5,5	95	7,89	5,5	2	0,166
2	4,6	140	9,94	3	1,16	0,053
3	1,6	140	2,1	1,1	1,56	0,016
4	3,7	170	21,76	3,8	1,6	0,09
5	4,1	205	12,3	5,5	0,93	0,075
6	3	140	39,2	4,9	1,44	0,066
7	3,6	210	11,13	3,2	1,43	0,068
8	7,3	140	12,6	3,6	2,5	0,12
9	6,6	110	10,1	16	2	0,44
10	13	120	24	10	1,95	0,29
11	24,6	110	37,4	5,6	1,–	0,13
12	7,3	135	13,6	1	1,84	0,024
13	32,5	125	53,8	46,3	1,–	1,04
14	6,2	130	8,97	8,3	2,–	0,19
15	4,4	140	7,14	5,9	2,05	0,14
16	14,0	180	34,7	0,14	1,8	0,004
17	7,5	160	19,2	10	2,54	0,39

Table 5. Statistical evaluation of the specific accumulation (cpm/mg) based on the differences of paired organs and the Student's test of significance

Pairs of organs	No.	Mean of the differences	Variance of the differences	Standard deviation	T-test temp.	tab.	Level of	Result of the significance test
Liver/spleen	17	1,215	57,165	7,561	0,663	0,535	60 %	– –
liver/kidney	16	8,313	68,042	8,249	4,031	3,286	0,5 %	++++
liver/adrenal	16	7,113	61,842	7,864	3,618	3,286	0,5 %	++++
liver/pancreas	15	5,445	96,013	9,799	2,152	2,145	5 %	+
liver/mesenterial lymph node	15	7,077	89,899	9,483	2,891	2,624	2 %	++++
liver/heart	17	8,057	78,461	8,854	3,792	3,252	0,5 %	++++
liver/lung[+]	13	9,034	87,602	9,360	3,480	3,428	0,5 %	++++
liver/thymus	16	7,293	58,187	7,628	3,824	3,286	0,5 %	++++
liver/thyroid	10	11 889	92,609	9,623	3,743	3,690	0,5 %	++++

[+]false high values of the lung due to contamination have been considered

Noteworthy is the following fundamental finding: The quantitative extent of lymphonodular accumulation of ^{198}Au-colloid is independent of the weight of each single nodule i.e. only governed by the phagocytic ability of lymph node tissue. Therefore the result can be regarded as an illustration for the fact that scintigraphically reduced or lacking radioactivity represents only an uncertain criterion of neoplastic involvement in lymph node scintigraphy (30). Practical application in man for exploring lymph flow in the upper direction has been referred to previously (17).

Furthermore, the importance of our results may be seen in the previously unknown fact that the greater omentum is a second mainly lymphatic pathway away from the peritoneal cavity in rabbits. Although this uptake of inactive particles in different mammals and humans has been well demonstrated in earlier studies (6, 13, 27, 28) and the opacification of the lymphatics in the greater omentum was proved by *Shdanow* (26), the lymphatic drainage and storage function of the organ never before have been documented either scintigraphically or by X-ray methods.

We consider it worth emphasising, that the storage function of the total major omentum is nearly the same quantitively as that of all mediastinal lymph nodes in one animal. This fact, however, should not be identified with its drainage function, which has, as yet, not been measured likewise. The main drainage channels leading the lymph away from the omentum are still completely unknown. A detailed description of the existant lymphatic network of the greater omentum was given just a few years ago by *Nylander and Tjernberg* (21).

The resorptive ability of the greater omentum has also been confirmed for human beings in the treatment of chronic lymphedema by omental transposition (11). Intraperitoneal application of radionuclides leading to "paraselective" accumulation within the regional lymphatics and producing an intensive irradiation of the mediastinal lymph nodes and the greater omentum may be useful for radiotherapy.

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