The Influence of Intra-arterial Administration of Histamine upon the Circulating Leukocytes of Man

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THE DISAPPEARANCE of circulating leukocytes within the pulmonary circulation during forced expiration,[1] and following the intravenous administration of histamine[2] or saccharated iron oxide,[3] has created interest in the elucidation of the actual mechanism involved. Leukocytes, erythrocytes and platelets may accumulate in the capillaries of many organs under specific circumstances.[4-6] Silverman[7] attributed some leukopenias to the filtration of leukocytes due to mechanical obstruction induced by endothelial swelling of the capillary wall. Sudden hypotension is also associated with a decrease in the number of circulating leukocytes in the arterial blood which has been attributed to an increase in the capability of the leukocytes in adhering to the walls of vessels when the blood flow is slowed.[8, 9] The erythrocytes are not similarly affected. Vejlens[10] similarly found an increased margination of leukocytes in the vascular stream of rabbits due to increased adhesiveness of the leukocytes as the flow of blood was slowed.

Schwenkenbecher and Siegel[11] found variations in leukocyte count from different vessels significantly beyond the limits of technical errors; the counts were done with meticulous care and at frequent intervals. Previous studies[1] had shown that the leukocyte count in venous blood of the upper or lower extremities is almost always significantly different from the simultaneous arterial leukocyte count.

Although it is generally conceded that the capillary bed of the lung, liver and spleen are heavily endowed with a special form of endothelial cell (macrophage, Kupffer cell, etc.) which performs a major function in the reticulo-endothelial system, it is also known that under the proper circumstances, the vascular endothelium of the capillaries in practically any location is also capable of similar activity.[6, 12] Since the pulmonary capillaries are the first vascular bed to receive histamine when administered intravenously, it appeared desirable to study another capillary bed following the arterial administration of this substance. In an effort to investigate the capacity of the peripheral capillaries to remove leukocytes selectively from the circulating blood in man, the lower extremity was studied directly.

Subjects and Methods

Ten patients with wide-spread neoplastic diseases in relatively good condition and with apparently normal peripheral circulation were studied. Histamine phosphate was adminis-

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tered into the femoral artery on five occasions and into the aorta nine times at various levels. Rates of infusion from 1.1 to 13 μg. per second were employed. The influence of intravenous administration of histamine upon the circulating leukocytes[2] served as a control for interpretation of later changes in the arterial blood.

Initially, the femoral artery and vein in two patients were isolated surgically and samples were obtained directly from both artery and vein by cannula. Percutaneous sampling by indwelling large bore needles was employed in the remaining three studies on the extremities. Histamine phosphate, 0.1 to 0.3 mg. as base, diluted in isotonic saline, was administered through a #21 needle into the artery distal to the sampling site for the arterial blood, at uniform rates over a 30 second to 4 minute period. Samples of both venous and arterial blood were taken simultaneously every 30 seconds for 5 minutes and then every minute for an additional 5 minutes.

In 6 patients on nine occasions, histamine, 0.15 to 0.4 mg., as base, was administered into the aorta at different levels by intra-arterial catheter[13] and samples from the aorta and the pulmonary artery or inferior vena cava were taken simultaneously and frequently on the same time schedule. In two instances a second dose of histamine was administered shortly after the first dose.

Samples were collected directly into clean glass tubes containing 0.2 mg. of liquid heparin. All counts were made directly from the heparinized samples as promptly as possible, utilizing National Bureau of Standards certified hemocytometers and Trenner automatic filling pipets, with uniform agitation of all filled pipets for 10 minutes in an automatic rotator. At least 600 cells were counted for total numbers of cells, averaging the results of confirming duplicate chambers. For counts of 5000 to 10,000 leukocytes per cu. mm., counting all 9 squares on each of 2 chambers from a single pipet, the 70 per cent confidence limits of the value obtained are ±8.5 per cent. This ignores the added significance of serial results.

Results

In general, the intra-arterial administration of histamine was followed by a leukopenia which occurred first in the peripheral venous blood or simultaneously in both pulmonary artery and aortic blood. During the return of the leukocyte count toward normal, the arterial leukocytes significantly outnumbered those in the venous blood in 6 of the 11 studies.

Administration of Histamine into the Femoral Artery

Immediately following the administration of 0.1 to 0.3 mg. of histamine phosphate at rates of 1.1 to 6.7 μg. per second into the femoral artery, a marked decrease in the leukocyte number in femoral venous blood was observed in all 5 patients (table 1). The onset of this leukopenia in the venous blood generally occurred promptly following the start of the injection, reaching its nadir at 90 to 210 seconds with a rapid return after the end of the infusion (table 1, fig. 1). In four of five instances the leukopenia in the femoral venous blood preceded the arterial change in count. In the remaining study, the leukopenia occurred simultaneously in the femoral artery and vein. When changes in leukocyte level occurred in the femoral arterial blood, it was significantly less than that observed in the femoral venous blood samples in all instances. The changes occurred primarily in the granulocytes. When the administration of histamine was protracted, the leukopenia was accordingly prolonged until the conclusion of the injection (fig. 2). The severity of the leukopenia appeared to be related more directly with the rate of administration of histamine rather than the total dose.

TABLE 1.—*Hematologic Data on Administration of Histamine into the Femoral Artery in Five Patients*

Name	Sex	Age	Diagnosis	Wt. of patient (Kg.)	Dose (mg.)	Duration (sec.)	Rate of administration (μg. sec.)	Control WBC	Initial leukocyte change	%	Time (sec.)	Nadir	%	Time (sec.)
FAW*	M	27	Neurofibromatosis	49	0.3	0–285	1.1	5900	5000	18	30	4600	22	150
								6700	5600	16	30	5600	16	30
WEB*	M	23	Malignant melanoma	54	0.2	0–120	1.7	18,600	15,800	21	75	8400	55	210
								20,000	13,400	33	100	12,000	40	130
DEL*	F	40	Carcinoma cervix	57	0.2	0– 45	4.4	12,800	8100	37	60	7900	38	90
								13,600	10,800	20	90	10,800	20	90
GOO†	M	27	Anaplastic carcinoma	46	0.1	0– 20	5	10,200	7100	30	105	5500	45	155
								10,100	8200	19	120	8200	19	120
LAN†	M	34	Carcinoma kidney	78	0.2	0– 30	6.7	7800	5700	28	25	2300	71	150
								8800	7800	11	30	6100	24	120

* Site of injection, right femoral artery; sample sites, right femoral vein and artery.
† Site of injection, left femoral artery; sample sites, left femoral vein and artery.

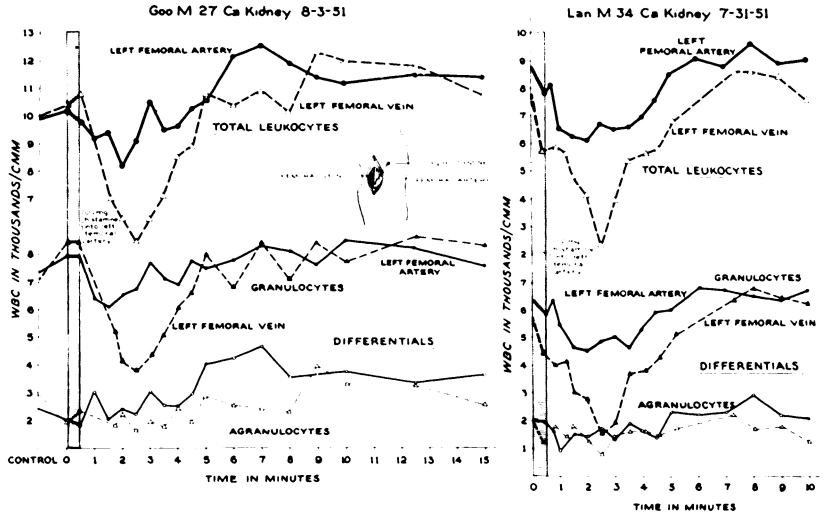

FIG. 1.—Simultaneous leukocyte counts from femoral artery and vein. Similar leukopenias following intra-arterial administration of 0.1 and 0.2 mg. Note more profound fall in venous leukocyte number occurring predominantly in the granulocytes.

Intra-aortic Administration of Histamine

When histamine was administered directly into the aorta at levels from T_3 to L_2, the decrease in leukocyte numbers in the venous blood preceded or occurred at approximately the same time as that sampled from the aorta in five of nine

TABLE 2.—*Hematologic Data on Nine Administrations of Histamine into the Aorta of Six Patients*

Name	Sex	Age	Diagnosis	Wt. of patient (Kg.)	Dose (mg.)	Duration (sec.)	Rate of administration (μg./sec.)	Site of injection	Control WBC	Initial leukocyte change	%	Time (sec.)	Nadir	%	Time (sec.)
KEB	M	52	Carcinoma lung	76	0.15	0–20	7.5	Aorta at T_3*	10,900	9500	−13	60	8000	−27	90
									12,000	10,800	−10	30	8100	−33	120
					0.15	120–145	10		8900	10,300	+16	150	13,600	+53	10 min.
									8100	9400	+14	150	13,600	+68	10 min.
PUL	F	64	Carcinoma pancreas	44	0.2	0–25	8	Aorta at L_2†	7900	6500	−18	30	4600	−38	90
									8200	6900	−16	30	3900	−52	90
									8600	7500	−13	30	4600	−47	90
MAR	M	51	Carcinoma lung	65	0.2	2–25	8.7	Aorta at T_4‡	9800	8400	−14	30	8400	−14	30
									9900	9500	−4	30	9200	−7	60
VAN	M	59	Multiple myeloma	64	0.2	0–20	10	Aorta at T_4*	4700	3700	−21	60	1100	−77	120
									6400	4800	−25	30	4600	−25	120
WEB	M	23	Malignant melanoma	60	0.3	0–25	12	Aorta at T_3*	9900	6200	−37	60	6200	−32	60
									10,200	8700	−15	36	5700	−44	90
VAN	M	59	Multiple myeloma	62	0.3	0–25	12	Aorta at T_8*	5500	6300	+14	30	4200	−24	60
									5200	3700	−29	60	3400	−35	120
					0.15	180–205	6		4600	4000	−13	330	4000	−13	330
									4900	3800	−22	270	3800	−22	270
CLI	F	55	Multiple myeloma	63	0.4	5–20	13	Aorta at T_7*	2600	2100	−19	90	2100	−19	90
						35–50	13		2800	3000	+47	30	2600	−7	90

* Sample sites, pulmonary conus and aorta.
† Sample sites, pulmonary conus, inferior vena cava, and aorta.
‡ Sample sites, inferior vena cava and aorta.

occasions (table 2, fig. 3). In four instances, the leukopenia in the aorta exceeded that in the blood from the pulmonary artery. In 1 patient with multiple

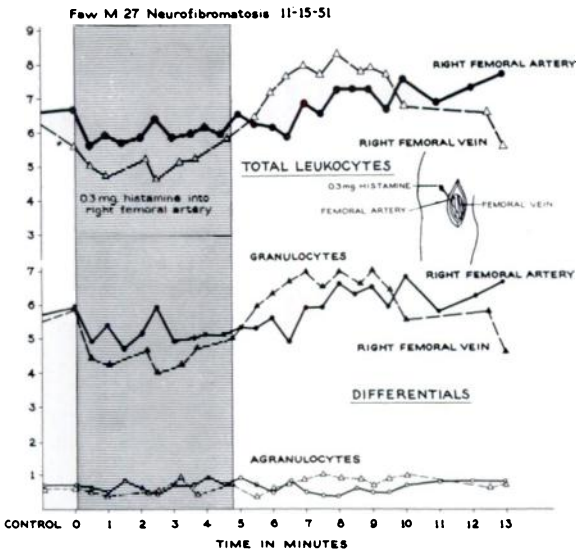

FIG. 2.—Depression of venous leukocyte number during the period of histamine administration at a slow rate of 1.1 μg. per second. Again the leukopenia is exclusively granulocytic in character.

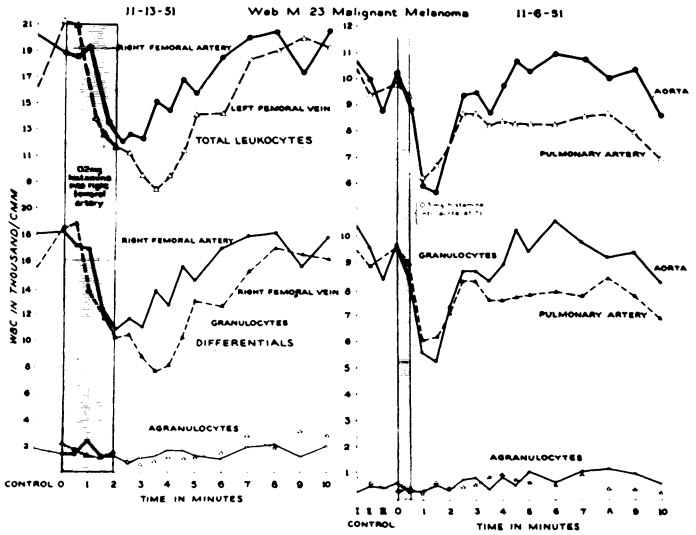

FIG. 3.—Comparison of leukopenias following administration of histamine at different rates into the femoral artery and aorta in the same patient.

myeloma (VAN) the intra-aortic administration of histamine at T_4 produced a profound leukopenia in the blood sampled from the pulmonary artery. Two weeks later administration of histamine at T_8 at a similar rate resulted in a less

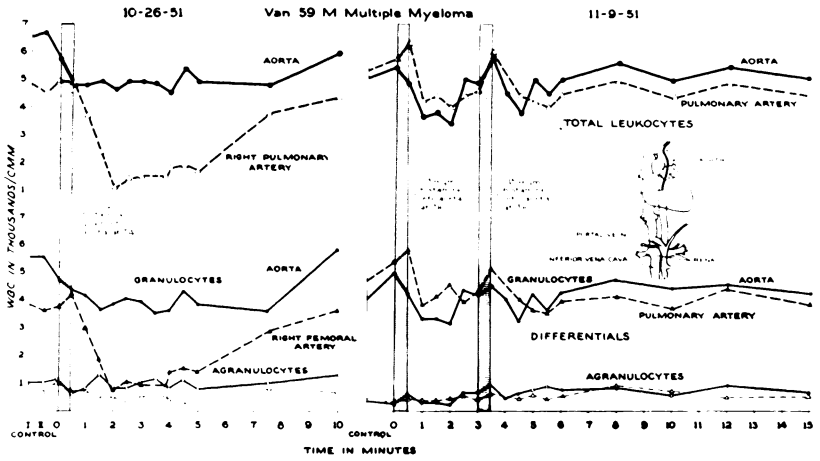

FIG. 4.—Comparison of response of intra-aortic histamine administration at T_4 and T_8 in a patient with multiple myeloma.

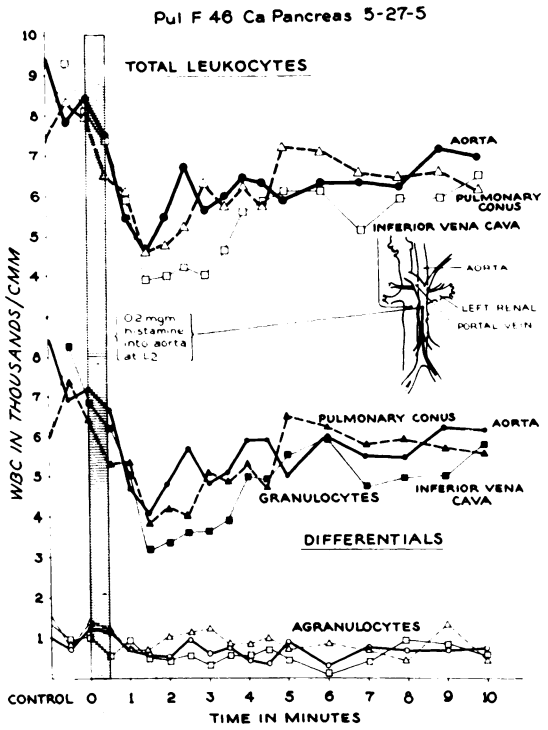

FIG. 5.—Appearance of leukopenia following administration of histamine distal to the celiac and renal arteries. The leukopenia in the blood sampled from the inferior vena cava was more profound than that from the other sites and least in the blood sampled from the aorta at L_2.

profound leukopenia favoring the arterial samples (fig. 4). In 2 patients (MAR and CLI) a slight fall in leukocyte count in the venous blood occurred without a change in the arterial leukocyte number. In 1 patient (PUL), the decreased

leukocyte number in the blood from the inferior vena cava was more profound and persisted longer and at a lower level than that observed in the blood samples simultaneously from the aorta and pulmonary conus (fig. 5).

In four instances in which it was studied, the hematocrit showed no significant changes. In general, the fall in leukocyte count was related particularly to the rate of administration rather than the total dose. The more rapid rates of histamine infusion were generally associated with the more profound leukopenias.

Discussion

The intra-arterial administration of histamine is presumed to cause a dilatation of all responsive vessels in the lower extremities, accompanied by a slowing of the blood flow. Hypotension was evident shortly after the histamine administration into the femoral artery and often the blood would not flow easily from the indwelling venous needle unless drawn by syringe. The marked difference in fall of leukocyte count in the venous blood with relatively little change in the arterial leukocyte content indicates a withdrawal of leukocytes somewhere within the circulation of the lower extremity. The differential leukocyte counts show that the major withdrawal occurred in the granulocytes, perhaps because of the predominance of these cells.

The arterial leukopenia is attributed to the withdrawal of leukocytes in the pulmonary circulation due to the histamine which traversed the peripheral circulation from the site of intra-arterial administration.[2] The simultaneous venous leukopenia is attributed to the removal of leukocytes in the peripheral vessels. The maintenance of the arterial leukocyte level in those instances when the venous inflow of leukocytes was significantly less is probably related to the pulmonary reservoir.[14]

The sequestration of leukocytes in the peripheral capillary bed of man following the arterial administration of histamine bears some relationship to the amount of histamine administered, but no consistent proportion of dosage to the number of cells removed could be defined. When an arterial leukopenia occurred during the intra-aortic administration of histamine, the arterial leukocyte level returned toward the control levels promptly thereafter and well before the venous counts. The only persistent arterial leukopenia occurred during the period of protracted administration of histamine.

Vejlens[10] described the marginal position of leukocytes with reduced velocity of blood flow. He also found margination to occur in rabbits subsequent to gelatin infusions without altering the viscosity of the blood stream. The polymorphonuclear leukocytes were affected far more than the lymphocytes. Slowing of blood flow may occur following the intra-arterial administration of histamine due to the direct vasodilation, and the withdrawal of leukocytes is attributed to this phenomenon aided by some alteration of clotting which may have further accentuated the adhesiveness of the leukocytes for the capillary walls.[2] The direct quantitative relationship of rate of intra-arterial administration of histamine to the development of the leukopenia is an approximate one in most instances, yet not inviolate. The peripheral circulation has exhibited a marked capacity to withdraw leukocytes selectively from the circulating blood under the influence of histamine, similar to that observed in the pulmonary circulation.

The leukopenia following the intra-aortic administration of histamine was essentially the same whether the level at which the histamine was introduced was proximal or distal to the celiac artery which seems to deny any major role of the portal organs in this leukocyte change.

The leukopenic effects of histamine upon the peripheral and pulmonary capillaries are similar, and the development of an arterial or venous leukopenia is apparently determined by the capillary bed which first receives the material in effective concentration. The leukopenia following either intravenous or intra-arterial administration of histamine is probably a result of withdrawal of leukocytes from the circulation by many capillary beds both peripheral and central. Thus the absence of a leukopenia following the administration of histamine to patients with lymphatic leukemia cannot be attributed solely to a failure of response of the pulmonary capillaries alone but must also include the peripheral capillaries.[15]

Summary

1. The leukocyte content of femoral arterial and venous blood was determined simultaneously following the administration of 0.1 to 0.3 mg. of histamine (as base) directly into the femoral artery in 5 patients at rates varying from 1.1 to 6.7 μg. per second.

2. A marked and prompt decrease in leukocyte number was found in the blood from the femoral vein of the same leg after the histamine infusion started; this preceded the changes in the blood from the femoral artery.

3. The discrepancy between the venous and arterial counts indicates the withdrawal of leukocytes within the circulation of the lower extremity which is generally related to the rate and amount of histamine administered.

4. In 6 patients, histamine (0.15 to 0.4 mg.) was administered directly into the aorta at levels from T_3 to L_2. In five of nine instances, blood from the pulmonary artery or inferior vena cava initially showed a prompt fall in leukocyte number, which exceeded the leukopenia observed in blood sampled from the aorta. In two instances, the leukocyte counts from the aorta exhibited no significant change.

5. The venous leukopenia following the administration of histamine into the aorta probably occurs as a result of sequestration of leukocytes in the peripheral capillaries which accompanies the arterial leukopenia due to a similar effect in the pulmonary circulation.

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