The Effect of Intravenous Histamine Administration on the Level of the White Blood Count in the Peripheral Blood*

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The pulmonary circulation has been shown to contain a mechanism capable of removing leukocytes from the peripheral blood. The method of demonstration of this removal mechanism entailed the rapid infusion of large numbers of leukocytes from a donor of the same blood and Rh type and sampling appropriate venous and arterial sites for the infused cells. The obvious limitations and difficulties of such a technic made it expedient to develop other more simple methods of inciting the lung removal mechanism. A just criticism of the infusion experiments is that the removal of leukocytes foreign to the host is studied. Furthermore, the infusion of such heterologous cells might also include substances from ruptured cells which were responsible for the removal mechanism. For these reasons various phenomena associated with prompt and transient leukopenias were considered for their influence upon this mechanism within the pulmonary circulation.

In anaphylaxis, a histamine-like substance is presumably released, respiratory difficulty ensues and a prompt marked leukopenia appears. Webb showed that anaphylaxis in dogs was associated with the sequestration of great numbers of leukocytes in the pulmonary capillaries and concluded that the engorgement within the lungs was largely responsible for the leukopenia that is characteristic of this state.

The lungs contain more histamine than any other single organ in the body, and as might be expected, also considerable quantities of histaminase. The source of the histamine in the lungs is obscure at present but it is known that most of the histamine content of whole blood is found in the myeloid cells. In patients with myelogenous leukemia, the histamine content of whole blood is usually elevated and has been recorded to be as high as 2.3 mg. per cent. Despite this large amount of circulating histamine, the substance appears to be inactive and fixed within the cell.

The mechanism of production of the leukopenia known to occur following intravenous administration of histamine was investigated primarily because of the similarity of histamine reactions and symptoms of anaphylactic shock. The

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leukopenia may be extreme, but is usually transient and the preinjection level of leukocytes is usually regained within 10 to 15 minutes. Since it occurs during the period of hypotension which often accompanies the intravenous administration of histamine, the leukopenia has generally been considered to be due to sequestration of the cells in the capillaries of the liver, spleen and gastro-intestinal tract, due to the diminished rate of blood flow resulting from the hypotension and vasodilatation.

SUBJECTS AND METHODS

Twelve patients with various advanced metastatic neoplastic diseases, but in relatively good general condition, were selected for this study. A No. 8, 9 or 10F cardiac catheter was passed into the outflow tract of the right ventricle or into the pulmonary conus and kept patent by a slow continuous drip of normal saline. On four occasions venous blood was sampled at the cubital vein site. A No. 18 or 19 gauge needle was placed in the brachial artery opposite from the arm into which the venous catheter had been introduced. In 4 studies the femoral artery was employed. In 1 patient (S. E.) catheters were introduced into both the right and left ventricle.

Histamine phosphate,* in doses of 0.1 to 0.3 mg. calculated as base, diluted in 1:10 cc. of normal saline, was injected intravenously at a constant rate during 10 to 60 second periods. Separate samples, both arterial and venous, were taken simultaneously at frequent intervals during the acute phase of the injection and for 10 to 30 minutes thereafter.

Blood samples were collected in 5 cc. tubes containing 2 mg. of liquid heparin as the anticoagulant. Leukocyte counts were performed promptly with National Bureau of Standards certified Trenner automatic filling pipets and National Bureau of Standards certified hemocytometers, counting all squares in double chambers. Clotting times were done in both glass and silicone-lined tubes.

RESULTS

Fourteen investigations of the response of the number of leukocytes in arterial and venous blood during and following the intravenous administration of histamine were completed in 12 patients (table 1). A prompt fall in the leukocyte level significantly below the control count occurred in all but 2 patients. There was no significant variation in the erythrocyte count or hematocrit. The leukopenia was transient, exhibiting a return toward the original level of white blood count within 3 to 10 minutes (figs. 1 and 2). During the leukopenia the decrease of leukocytes in the arterial blood samples preceded that in the venous blood by 20 to 180 seconds, except in 1 patient (S. E.) where the arterial leukopenia, although more severe, coincided with the venous leukopenia (fig. 3). In most instances a slight increase in leukocytes in the venous blood samples developed within 40 seconds after the start of the injection of histamine. The arterial-venous difference in the number of cells occurred primarily in the polymorphonuclear cells because of the larger number of these cells involved, although a similar leukopenia occurred percentage-wise in the lymphocytes in all but 2 of the 10 patients who showed a leukopenic response to histamine. Because of the relatively few cells involved, the differences between arterial and venous blood agranulocytes were not as great nor as significant by statistical standards. The leukocyte

* Histamine acid phosphate, 2.75 mg. per cc. (equivalent to histamine 1.0 mg.). Kindly furnished for this study by Eli Lilly & Company.
count in the arterial blood exceeded that in the venous blood during the return toward the control level. In most instances this predominance was maintained until the control level was approached.

A marked decrease occurred in the silicone clotting time immediately after the intravenous administration of histamine in the 3 patients in which it was studied (fig. 4). In 2 of these patients, the decreased clotting time was also found with unsiliconed glass tubes. There was no consistent significant change in the platelet count in either the venous or in the arterial blood of 3 patients so studied. Qualitative changes in the platelets were not investigated.

Almost all patients developed the usual clinical symptoms and signs following

| No. | Exp. | Patient | Sex | Age | Diagnosis                         | Histamine IV. Dose mg. | Time sec. of inj. | Control leukocyte count in thousands/cu.mm. Artery | Control leukocyte count in thousands/cu.mm. Vein | Maximum drop in WBC | Average number leukocytes removed per cu.mm. Artery | Time sec. | Average number leukocytes removed per cu.mm. Vein | Time sec. | Period of removal sec. |
|-----|------|---------|-----|-----|-----------------------------------|------------------------|-------------------|-----------------------------------------------|-----------------------------------------------|-------------------|-------------------------------------------------|-----------|------------------------|
| 1   | S. R. | M       | 71  |     | Mycosis fungoides                | 0.1                    | 20                | 4.0 4.5 40 70 43 160                          | 900 96                                        |                   |                                                 |           |                        |
| 2   | S. R. | M       | 66  |     | Carcinoma of bladder            | 0.2                    | 40                | 3.8 3.7 47 93 35 155                          | 550 80                                        |                   |                                                 |           |                        |
| 3   | R. M. | M       | 23  |     | Hodgkin's disease               | 0.2                    | 10                | 6.1 7.0 24 80 31 133                          | 750 90                                        |                   |                                                 |           |                        |
| 4   | O. H. | M       | 48  |     | Multiple myeloma                 | 0.3                    | 30                | 3.6 3.4 28 120 41 90                          | 450 60                                        |                   |                                                 |           |                        |
| 5   | J. K. | M       | 47  |     | Carcinoma of stomach            | 0.3                    | 30                | 3.1 3.3 29 70 42 120                          | 410 85                                        |                   |                                                 |           |                        |
| 6   | J. K. | M       | 28  |     | Embryoma of testicle            | 0.3                    | 30                | 4.7 4.2 45 60 30 120                          | 1075 132                                      |                   |                                                 |           |                        |
| 7   | S. P. | M       | 50  |     | Renal carcinoma                  | 0.3                    | 30                | 6.2 4.5 39 60 28 150                          | 300 30                                        |                   |                                                 |           |                        |
| 8   | J. Z. | M       | 55  |     | Lymphosarcoma                    | 0.3                    | 60                | 6.7 8.1 None None None                        | None                                         |                   |                                                 |           |                        |
| 9   | K. M. | F       | 24  |     | Carcinoma of rectum             | 0.3                    | 60                | 1.7 1.6 40* 120 60 150                        | 150* 105                                      |                   |                                                 |           |                        |
| 10  | B. G. | M       | 18  |     | Osteogenic carcinoma             | 0.3                    | 60                | 7.3 5.7 54 60 30 150                          | 1000 75                                       |                   |                                                 |           |                        |
| 11  | R. G. | M       | 20  |     | Von Recklinghausen's disease     | 0.3                    | 60                | 4.8 5.5 66 80 63 100                          | 970 160                                       |                   |                                                 |           |                        |
| 12  | A. K. | F       | 32  |     | Lymphatic leukemia               | 0.3                    | 60                | 185.0 150.0 None None None                    | None                                         |                   |                                                 |           |                        |

* 71% decrease in WBC between insertion of catheter into right ventricle and just prior to histamine injection.
† This is time from start of injection.
intravenous histamine administration, the severity of the reaction being dependent upon dose of histamine. These consisted of apprehension, headache of varying severity, dyspnea, transient hypotension, tachycardia, paresthesias and flushing. In the 2 patients in whom no change in leukocyte level occurred, the respiratory symptoms were negligible. In 2 patients (J. K. and S. P.) severe pain
devolved in the region of their intra-abdominal neoplasm immediately following the intravenous administration of 0.3 mg. of histamine.

In 1 patient (K. M.) the initial venous leukocyte count before catheter manipulation was 6,200 per cu. mm. Minutes later, immediately after the catheter had been placed in the pulmonary artery, the count was 1,600 per cu. mm. Despite this low count, a fall of 40 per cent in the leukocyte count was demonstrated following histamine.

Of the 2 patients who exhibited no alteration in the peripheral leukocyte

![Graph showing leukocyte counts](image-url)
count, 1 patient (J. Z.) had lymphosarcoma, untreated, with 14,000 leukocytes per cu. ml. with only 16 per cent lymphocytes in the peripheral blood and 93 per cent lymphocytes in the bone marrow. The other patient had lymphatic leukemia, with a leukocyte count of 185,000 per cu. mm. and a bone marrow aspiration revealed 77 per cent lymphocytes.

Fig. 2.—Immediate arterial granulocytopenia preceding the fall in the right ventricular leukocyte number by 90 seconds. In this case the lymphopenia occurred as the granulocytes were increasing and no significant arterial-venous difference was demonstrable. The upper half of the chart refers to the total leukocyte count; the lower half illustrates the differential counts.

**DISCUSSION**

The sampling of blood from the venous and arterial sites permitted observation of the flow of formed elements of the blood into and from the pulmonary vascular circuit. The immediate decrease in number of leukocytes in the arterial blood appeared at least one or two circulation times before the fall in the venous blood count, and indicated that the leukocytes were being withdrawn between the venous and arterial sampling sites. The lungs are the only organ capable of such removal of leukocytes, although the left heart and large vessels might possibly be implicated. The sampling sites were chosen in these patients so that the lungs were, for all practical purposes, isolated between the two sites. The sites used in patient S. E. excluded most of the large vessels leading to or from the heart. The arterial-venous difference in leukocyte count was not as apparent as with larger doses, but this is attributable to the fact that this patient received
only 0.1 mg. of histamine. The fall in leukocyte number in the arterial blood was from 7,000 to 4,000 while the venous blood count fell from 6,000 to 4,000 and the arterial-venous difference was clearly shown at the nadir.

The lungs retained the cells for only 50 to 150 seconds. The flow of cells then changed from withdrawal to delivery of cells into the arterial blood from the pulmonary circulation, since the arterial leukocyte count exceeded that on the venous side. It is postulated that most of these cells are those which had just previously been sequestered in the lungs. The increase of cells in the arterial blood could also be due to new cells produced, retained or residing in the lungs from some previous period.

The leukocyte count in 1 patient (K. M.) decreased from 7,000 to 1,500 shortly after the catheter was manipulated into the pulmonary artery. Similar decreases were noted on other occasions although none so marked as in this patient. No consistent changes in the count occurred once the catheter was placed in the pul-

![Graph showing leukocyte counts over time.](image)
monary artery. It is possible that mechanical stimulation of the pulmonary artery in some manner incites the leukopenia.

The bone marrow of both patients who failed to show a leukopenia following histamine exhibited a predominance of lymphocytes. One of these patients (A. K.) was a frank lymphatic leukemia with an absolute lymphocytosis. The only patients who have failed to demonstrate a removal mechanism in the lung as demonstrated by cell infusion or cross transfusion technics have also been leukemic.

![Diagram](image_url)

**FIG. 4.**—Prompt decrease in clotting time of arterial blood in siliconed tubes immediately following intravenous histamine with prolongation of the venous clotting time before it approached the clotting time of the arterial blood.

The increased rate of coagulation of the blood following the histamine was dramatic and possibly responsible for the lung leukocyte removal observed under these conditions. The blood tended to clot in the arterial cannula which caused loss of some samples and the discarding of two additional studies because the data were incomplete. The information that was obtained, however, coincided with these reported studies. It could be postulated that the smaller capillaries of the lungs may have been plugged by thrombi or changes in viscosity of the blood and the leukopenia caused by the resultant trapping of the leukocytes.
This, however, would not explain the mechanism of the release of white blood cells from the lungs shortly thereafter since the short clotting time persisted.

The change in coagulability suggests an increase in coagulation factors, e.g., thromboplasmin, coagulation accelerator substances, or alteration in quality of platelets without change in number. The reduction in clotting time is in apparent contradiction to that found in anaphylaxis in other animals. In anaphylaxis in the dog, a histamine-like substance is released and the blood becomes incoagulable, but this is not true in the rabbit or guinea pig.\textsuperscript{3-15} Such species differences make data from animals difficult to extrapolate to man. Intravenous histamine is reported to increase the disintegrative ability of the platelets which may be largely responsible for the more rapid clotting.\textsuperscript{16} There is also some evidence that an equilibrium exists between circulating histamine and heparin which controls the inactivation of thrombin and thus influences coagulation.\textsuperscript{17}

Code\textsuperscript{18} has shown that the histamine in the blood is largely contained within the granular leukocytes. Variable quantities of histamine activity were obtained from rabbit "platelet" material which suggested contamination of the platelet deposits with fragments of the more fragile leukocytes.\textsuperscript{18} It is conceivable that as the granulocytes circulate in the peripheral blood, they disintegrate or are removed in the lung by the normal homeostatic mechanism with a release of this histamine-like substance which may further aid the lung removal mechanism and also enhance the coagulation properties of the blood by increasing or maintaining the disintegrative ability of the platelets. One must also consider the possibility that fragments of the granulocytes broken down in the lung may appear in the arterial blood as platelets or platelet-like bodies. This has been observed during cross transfusions in man.\textsuperscript{19}

The intravenous administration of deliberately fragmented leukocytes to rabbits has been shown to cause a severe leukopenia\textsuperscript{20} which may in part be due to the amount of liberated histamine contained in this cell mass although these investigators felt it was due to some other substance.

Histamine causes vasodilation of the systemic vessels resulting in hypotension which, however, is associated with pulmonary arterial hypertension due to pulmonary arteriolar constriction with a decreased cardiac output.\textsuperscript{3-4} The blood flow through the lungs consequently is slowed which may accentuate the leukopenia but cannot explain the lack of fall in the erythrocytes and platelets.

Another possible explanation exists for the removal of leukocytes, particularly granulocytes, in the pulmonary circulation following histamine. During reduced velocity of the blood flow in the capillaries, the polymorphonuclear cells take a marginal position. A relative increase in the adhesion of these cells to the capillary wall occurs due to the decreased force of the slowed blood stream to detach these leukocytes or prevent their sticking to the wall.\textsuperscript{21} The increase in coagulation should accentuate this effect. The lymphocytes only become marginal in small numbers and furthermore possess little adhesive capacity as compared to the polymorphonuclears.

Under the conditions of this investigation, the lungs are maximally capable of removing an average of 720 leukocytes per cu. mm. per minute from the circulation or a total of approximately four billion white cells during this time. There
appears to be some relationship between dosage of histamine, rate of administration and rate of removal of leukocytes but no direct proportionality could be established. The duration of the leukopenia may be determined by histaminase activity and other similar substances and their ability to inactivate histamine. A balance of such substances may be responsible for the lung removal mechanism resulting in the maintenance of a relatively stable leukocyte count. Leukocyte counts of arterial and right ventricular blood normally show a variation indicating a flow of white cells into and from the lungs. This ebb and flow of leukocytes may be the reflection of the control exerted to maintain homeostasis of the leukocyte level in the peripheral blood and may involve sites other than the lung, e.g., spleen, liver, gastro-intestinal tract, etc. Nevertheless, the lung mechanism appears to be equally if not more rapidly effective than any other site reported. The clear demonstration of this activity in the lung by the intravenous administration of histamine offers a simple method for further study of this mechanism. Whether this mechanism is identical with that originally observed by cell infusion studies remains to be determined.

SUMMARY

1. By simultaneously sampling venous and arterial blood by cardiac catheterization or vessel cannulation, the number of leukocytes entering and leaving the lungs was observed in 12 patients on 14 occasions.

2. The intravenous administration of histamine phosphate in doses of 0.1 to 0.3 mg. (as base) over 10 to 60 seconds, was accompanied by a prompt decrease in leukocyte number in the arterial blood 20 to 60 seconds before the venous white cell count fell. This was interpreted as demonstrating that the leukocytes were removed from the peripheral blood in the pulmonary circulation. The granulocytic series appeared to be more involved in the leukopenia, although a similar but less apparent change was noted in the agranulocytes.

3. The leukopenia persisted for 40 to 180 seconds following which the arterial leukocyte count exceeded that in the venous blood indicating a return of leukocytes from the lungs into the peripheral circulation.

4. The intravenous administration of histamine also resulted in an immediate decrease in clotting time as determined both by glass and siliconed tube techinics.

5. The intravenous injection of histamine affords a relatively simple technique to study one type of leukocyte removal mechanism present in the pulmonary circulation.

REFERENCES


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