INCREASED BLOOD LEVELS of histamine have been reported in patients in various stages of myeloproliferative disease. However, the relationship of this biochemical abnormality to the clinical manifestations and pathophysiology of these syndromes has not been established. The association of increased circulating levels of histamine in myeloproliferative disease with the frequent occurrence of symptoms referable to the pharmacologic effect of histamine suggests that a relationship between elevated histamine levels and some of these symptoms and complications exists in myeloproliferative disease. The purpose of this study was to measure histamine levels in a group of patients presenting with various phases of myeloproliferative disease (polycythemia vera, "spent" polycythemia, myeloid metaplasia, myelofibrosis), to study the relationship of elevated histamine levels to the presence of symptoms that may accompany an increase in circulating histamine, and to evaluate the effect of a potent histamine antagonist, cyproheptadine (Periactin), on these symptoms.

MATERIALS AND METHODS

The patients studied were part of a group comprised of ward, clinic and private patients with myeloproliferative disease who are being followed by the Department of Hematology of The Mount Sinai Hospital as part of a long-term study of this group of diseases. The criteria used to establish the diagnosis of polycythemia vera were the presence of an increased red cell mass measured with Cr-51 (in the absence of bleeding or phlebotomy), a normal arterial oxygen saturation, evidence of panmyelosis (leukocytosis and thrombocytosis), the presence of increased numbers of immature leukocytes and/or normoblasts in the peripheral blood, and splenomegaly as well as increased hematopoietic activity of bone...
GILBERT, WARNER AND WASSERMAN

marrow obtained by aspiration or biopsy), elevated alkaline phosphatase activity of the leukocytes, hyperuricemia, and an increase in serum vitamin B₁₂. The concurrence of an elevated red cell mass and splenomegaly was considered sufficient for the diagnosis. In the absence of splenomegaly, the addition of two or more of the parameters noted to the erythrocytosis was required to make a diagnosis of polycythemia vera. Cases of polycythemia vera were classified as “uncontrolled” when the hematocrit and red cell count exceeded 52 per cent and 6.5 million/cu. mm., respectively. This group consisted of untreated cases, those being treated with phlebotomy and/or myelosuppressive therapy (busulfan, chlorambucil, cyclophosphamide) without response, and those who had previously responded to therapy but were in relapse at the time of the study. The “controlled” group consisted of patients in whom the hematocrit and red cell count had been reduced to 52 per cent and 6.5 million/cu. mm. or below by treatment with myelosuppressive drugs.

The group classified as “spent” polycythemia, myeloid metaplasia and myelofibrosis included: (a) patients with previously diagnosed polycythemia vera who showed a decrease of the red cell mass to normal or lower levels in the absence of bleeding or treatment with myelosuppressive therapy, and increasing extramedullary hematopoiesis as evidenced by an enlarging spleen and/or liver and a leukoerythroblastic peripheral blood picture; (b) patients without an antecedent history of polycythemia vera who presented with splenomegaly and/or hepatomegaly, a leukoerythroblastic blood picture and normal or elevated levels of leukocyte alkaline phosphatase activity. The diagnosis of myelofibrosis was made when increased fibrous tissue was found in specimens obtained by bone marrow biopsy in patients with “spent” polycythemia or myeloid metaplasia.

A group of patients with “relative” polycythemia was also studied. The diagnosis of “relative” polycythemia was made in cases with persistently elevated hematocrit levels (exceeding 52 per cent), a normal red cell mass (measured with Cr₁₉) and the absence of any evidence of myeloproliferative disease or increased hematocell proliferation.

Histamine was measured using a spectrophotofluorometric determination as described by Shore et al. for blood, and by Oates et al. for urine. Blood histamine measurements were performed by extraction of histamine into butanol from alkalinized perchloric acid extracts of whole blood hemolysates, return to an aqueous phase and condensation with o-phthalaldehyde to form a fluorescent product which is estimated in a spectrofluorometer. Urine histamine was measured on eluates obtained from passage of acidified urine through a column containing a weakly acidic cation exchange resin (Amberlite IRC 50). The range of error of the blood determination is ±0.01 μg./ml. and for urine ±5 μg./24 hours. The mean and distribution of values for blood and urine histamine in a group of normal subjects and those with “relative” polycythemia are shown in Table 1.

Cell-rich fractions were obtained by collecting blood into plastic tubes containing one-tenth volume of Versene (1 per cent in 0.6 per cent saline). One-fourth volume of dextran (M.W. 75,000, 6 per cent in 5 per cent dextrose) was added and the supernatant was removed after sedimentation for one hour at 4 C. An aliquot was removed to serve as the platelet-rich fraction and the remainder was centrifuged at 225 g at 4 C. for 10 minutes. The resulting cell button was resuspended in cell-poor plasma (obtained by centrifuging an aliquot of supernatant at 2000 g for 20 minutes) to provide the leukocyte-rich fraction. The erythrocyte-rich fraction was pipetted from the bottom of the original collecting tube. In later experiments in which it was found unnecessary to remove platelets, cell-rich fractions were obtained by mixing 6 ml. of blood with 12 ml. of 3 per cent dextran (M.W. 250,000 made up in tris-buffered saline, pH 7.4) and 0.25 ml. of 5 per cent Versene in a siliconized test tube. After 20–30 minutes of sedimentation at room temperature, the supernatant was removed and centrifuged at 500 g for 10 minutes. The cells were resuspended and washed once in buffered Tyrode’s solution (pH 7.4). Cell counts were performed on all fractions using standard technics as described in Wintrobe. White cell differential counts were performed on smears of peripheral blood made at the time of the blood collection. Absolute basophil counts were performed on the peripheral blood and leukocyte-rich fractions using the technic of Moore et al.
HISTAMINE IN MYELOPROLIFERATIVE DISEASE

Table 1.—Blood and Urine Histamine Levels in Control Subjects (Normal and "Relative" Polycythemia) and Patients with Myeloproliferative Disease

<table>
<thead>
<tr>
<th>Blood Histamine µg./ml.</th>
<th>Normal Subjects</th>
<th>&quot;Relative&quot; Polycythemia</th>
<th>P. V. Uncontrolled</th>
<th>P. V. Controlled</th>
<th>&quot;Spent&quot; P. V., Myeloid Metaplasia, Myelofibrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>.01–10</td>
<td>67</td>
<td>20</td>
<td>11</td>
<td>28</td>
<td>5</td>
</tr>
<tr>
<td>.11–20</td>
<td>—</td>
<td>1</td>
<td>15</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>.21–30</td>
<td>—</td>
<td>—</td>
<td>3</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>.31–40</td>
<td>—</td>
<td>—</td>
<td>2</td>
<td>—</td>
<td>2</td>
</tr>
<tr>
<td>.41–50</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>.51–1.00</td>
<td>—</td>
<td>—</td>
<td>2</td>
<td>—</td>
<td>4</td>
</tr>
<tr>
<td>&gt;1.00</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>1</td>
</tr>
</tbody>
</table>

No. cases                  67                21              33               30               17

Mean blood histamine:

µg./ml.                   .04               .04              .19              .06              .36

Range                     .01–10            .02–13           .01–100          .01–19           .03–1.4

<table>
<thead>
<tr>
<th>Urine Histamine µg./24 hr.</th>
<th>11–30</th>
<th>31–50</th>
<th>51–70</th>
<th>71–90</th>
<th>91–110</th>
<th>111–130</th>
<th>131–150</th>
<th>&gt;150</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>5</td>
<td>5</td>
<td>7</td>
<td>4</td>
<td>2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| No. cases                  19               7               24               21               15

Mean urine histamine:

µg./24 hrs.                42               40              107              48              119


RESULTS

Blood and Urine Levels of Histamine

Table 1 shows the mean and distribution of blood and urine histamine levels in two groups of patients without myeloproliferative disease (normal subjects and "relative" polycythemia) and in patients with various phases of myeloproliferative disease. These data indicate that hyperhistaminemia and hyperhistaminuria are a frequent accompaniment of myeloproliferative disease, especially in uncontrolled cases and those with "spent" polycythemia, myeloid metaplasia and myelofibrosis. Of the 60 patients who had simultaneous studies of blood and urine histamine, two cases had elevated blood histamine in the presence of normal urine histamine and five cases had normal blood histamine with elevated urine histamine. In the remaining 53 cases the blood and urinary findings paralleled each other. In most of the cases studied, serial specimens were collected over a period of time ranging from several weeks to 3½ years. In a given patient there was little variation in blood and urine histamine in
Table 2.—Summary of Direct Basophil Counts in Normal Subjects and Patients with “Relative” Polycythemia and Myeloproliferative Disease

<table>
<thead>
<tr>
<th>Basophil Count/cu. mm.</th>
<th>Normal</th>
<th>“Relative” Polycythemia</th>
<th>P.V. Uncontrolled</th>
<th>P.V. Controlled</th>
<th>“Spent” P.V., Myeloid Metaplasia, Myelofibrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>10–63</td>
<td>7</td>
<td>6</td>
<td>4</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td>64–109</td>
<td>—</td>
<td>1</td>
<td>9</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>110–159</td>
<td>—</td>
<td>—</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>160–199</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>200–249</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>3</td>
</tr>
<tr>
<td>250–299</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>&gt;299</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>No. cases</td>
<td>7</td>
<td>7</td>
<td>18</td>
<td>22</td>
<td>7</td>
</tr>
<tr>
<td>Mean basophil count/cu. mm.</td>
<td>31</td>
<td>31</td>
<td>177</td>
<td>43</td>
<td>142</td>
</tr>
<tr>
<td>Range</td>
<td>21–63</td>
<td>9–75</td>
<td>34–826</td>
<td>10–113</td>
<td>38–225</td>
</tr>
</tbody>
</table>

Table 3.—Relation of Direct Basophil Count to Blood Histamine in 47 Patients with Myeloproliferative Disease

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>.01–.1</td>
<td>22</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>.11–.2</td>
<td>2</td>
<td>5</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>.21–.3</td>
<td>2</td>
<td></td>
<td>1</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>.31–.4</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>.41–.5</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>.51–.6</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>.61–.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

*Normal range.

the absence of a change in clinical status, either spontaneous or induced by treatment.

Localization of Blood Histamine

Cell-poor plasma was found to contain unmeasurably low or barely detectable quantities of histamine, even in patients with markedly elevated whole blood levels. The localization of cellular histamine in patients with myeloproliferative disease was studied by measuring the histamine levels of fractions containing varying numbers of leukocytes, erythrocytes and platelets. In 50 fractionations the leukocytes were found to be the major source of blood histamine.

The relationship of the number of basophils in the peripheral blood to the level of blood histamine was studied. Direct basophil counts were performed using a toluidine blue stain. Good reproducibility was obtained with this method, and serial basophil counts were unchanged in the same individual in the absence of a change in clinical status. Table 2 shows that elevated basophil counts were found in 50 per cent of all patients with myeloproliferative disease. Elevated counts occurred with the greatest frequency and were highest in patients with uncontrolled polycythemia, “spent” polycythemia, myeloid metaplasia and myelofibrosis. Table 3 shows the relation of the direct
HISTAMINE IN MYELOPROLIFERATIVE DISEASE

Table 4.—Occurrence of Symptoms in Patients with Myeloproliferative Disease

<table>
<thead>
<tr>
<th></th>
<th>No. Cases</th>
<th>Pruritus</th>
<th>GI Symptoms</th>
<th>Urticaria</th>
</tr>
</thead>
<tbody>
<tr>
<td>P.V. uncontrolled</td>
<td>33</td>
<td>52%</td>
<td>36%</td>
<td>12%</td>
</tr>
<tr>
<td>P.V. controlled</td>
<td>30</td>
<td>20%</td>
<td>10%</td>
<td>—</td>
</tr>
<tr>
<td>“Spent” P.V., Myeloid Metaplasia, Myelofibrosis</td>
<td>17</td>
<td>47%</td>
<td>35%</td>
<td>6%</td>
</tr>
</tbody>
</table>

Table 5.—Relation of Elevated Histamine Levels to Symptoms in Patients with Myeloproliferative Disease

<table>
<thead>
<tr>
<th>Histamine Level (No. of Cases)</th>
<th>Pruritus</th>
<th>GI Symptoms</th>
<th>Urticaria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (39)</td>
<td>10%</td>
<td>10%</td>
<td>—</td>
</tr>
<tr>
<td>Elevated (41)</td>
<td>66%</td>
<td>41%</td>
<td>12%</td>
</tr>
</tbody>
</table>

basophil count of the blood to its histamine content. A rough correlation between whole blood histamine and basophil count was found in normal subjects and in most cases of myeloproliferative disease. Similar results were obtained when white cell fractions were studied. However, several cases with myeloproliferative disease have shown, on repeated study, an increase in basophil counts without increased histamine levels; in still others histamine levels have been elevated in the presence of normal basophil counts. These observations suggest that the content of histamine in the basophil may be altered in myeloproliferative disease and that in some cases other granulocytes may contribute significantly to the total leukocyte histamine.

Effect of Treatment

As shown in Table 1, polycythemia vera in hematologic remission has a lower incidence of hyperhistaminemia and hyperhistaminuria than untreated or uncontrolled cases. Phlebotomy alone failed to produce any changes in blood or urine levels. Myelosuppressive drug therapy, however, resulted in a decrease in blood histamine and in reduced histamine excretion as control of the polycythemia was achieved. The decrease in blood histamine is not merely a reflection of the decrease in white cells produced by therapy, since the histamine level expressed as micrograms/10⁹ myeloid cells also fell after therapy.

Relation of Histamine Levels to Symptoms

The incidence of certain symptoms resembling the known pharmacologic effects of histamine was analyzed in patients with myeloproliferative disease. Patients were considered to have pruritus if they complained of repeated episodes of generalized itching occurring spontaneously or following a bath or shower. Gastrointestinal symptoms were considered present if the patient complained of pyrosis, midepigastric pain, acid eructations, vomiting or had x-ray evidence of active peptic ulcer. Table 4 shows the frequency of symptoms during the various phases of myeloproliferative disease. The occurrence of these symptoms with equal frequency in patients with “uncontrolled” polycythemia vera and “spent” polycythemia suggests that they are not solely a result of hypervolemia or increased viscosity. Table 5 compares the incidence
of pruritus, gastrointestinal symptoms and urticarial phenomena in patients with myeloproliferative disease with normal and elevated histamine levels. Patients with blood histamine values of 0.11 μg. or more per ml. whole blood or with urine histamine levels of 70 μg. or more per 24 hours were considered to be in the "elevated" category. This analysis shows an incidence of pruritus, gastrointestinal symptoms and urticarial manifestations of 7-fold, 4-fold and 12-fold greater in patients with elevated blood and/or urine histamine as compared with patients with normal histamine levels.

The Effect of a Histamine Antagonist on Symptoms

Cyproheptadine, 1-methyl-4, (5-dibenzo-[a-e] cycloheptatrienylidene)-piperidine hydrochloride monohydrate, an antihistamine-antiserotonin compound, has been found effective in the treatment of pruritic dermatoses believed to be due to the release of histamine or perhaps serotonin (urticaria, angioneurotic edema, poison ivy, insect bites)\textsuperscript{10,11} and has been shown to exert an inhibitory effect on histamine-induced gastric secretion in the dog.\textsuperscript{12} Cyproheptadine was administered to 18 patients with elevated blood and/or urine histamine (10 with uncontrolled and one with controlled polycythemia vera, six with “spent” polycythemia, myeloid metaplasia and myelofibrosis, and one patient who was studied during both the uncontrolled and the "spent" phase of polycythemia vera). Sixteen of the patients had pruritus, seven had upper gastrointestinal symptoms, and four had urticaria. One patient with controlled polycythemia and normal histamine levels who complained of mild pruritus was also studied.

The pruritus seen in patients with myeloproliferative disease is induced or increased in intensity by bathing or showering. Several patients were unable to expose their bodies to water and had to resort to regional sponging of small areas of the body. Other medications that had been used by these patients to control the pruritus consisted of antihistamines such as benadryl, pyribenzamine, and chlorpheniramine (3 cases), temaril (2 cases), librium (1 case), meprobamate (1 case), and prednisone (1 case). Prednisone gave moderate relief in one case during the six weeks of its administration, and in one patient pruritus was relieved by benadryl for one week but recurred despite its continued administration. In 12 patients cyproheptadine, given in 4 mg. doses 3 or 4 times daily, completely suppressed the pruritus induced by bathing or showering as well as any spontaneously occurring pruritus. In three patients spontaneous pruritus was suppressed and postbathing pruritus still occurred but was diminished in intensity and duration. Maximal suppression was produced when the medication was taken one-half hour before bathing. The two cases of controlled polycythemia vera with pruritus (one with normal and one with elevated histamine levels) experienced no relief from cyproheptadine. Patients complained initially of drowsiness, but in all cases this side effect disappeared after medication was continued for five to seven days. Some patients noted an increase in appetite. One patient was not included since she discontinued the medication after two doses because of drowsiness. Another patient (included above) had relief of pruritus, but stopped the drug after four days because of restlessness and insomnia. A diminution in the anti-
histamine in myeloproliferative disease

pruritic effect of cyproheptadine was noted in two cases after prolonged administration (6 months and 2 years).

Four patients had recurrent urticarial manifestations in the form of hives and giant urticaria. One of the patients had episodes of swelling of an arm or leg with vesicle formation and erythema of the skin in the involved area. If untreated, the swelling persisted for two to four days. When cyproheptadine was given, a response was seen in six to eight hours. In all four cases the recurrent urticarial attacks were suppressed by daily cyproheptadine administration.

Symptomatic relief was not accompanied by any change in levels of blood or urine histamine. This finding is compatible with the current understanding of the mode of action of cyproheptadine as an antagonist at the receptor site to the effects of histamine that has already been formed and released.

Evaluation of the Effects of in Vivo Histamine Release

Codeine has been found to be a histamine releaser in vivo. Since the evaluation of relief of symptoms after the administration of cyproheptadine has the limitation of being subjective, a codeine-provocative test was employed to obtain an objective evaluation of the degree of histamine release in these subjects and determine the histamine-antagonizing effects of the drug. Six patients with hyperhistaminemia and a history of pruritus were each given 30 mg. of codeine subcutaneously. All reacted by developing one or several wheals 2 to 6 cm. in diameter at the injection site, surrounded by an area of erythema varying from 4 to 9 cm. in diameter and accompanied by pruritus and a burning sensation locally. Two patients developed systemic symptoms of flushing, dizziness and headache. The local signs and symptoms developed over a period of five to ten minutes after injection, were maximal in one-half hour, and subsided in one to two hours. The patients were placed on daily cyproheptadine therapy and restudied at a time when they reported symptomatic relief from pruritus. In all six patients there was suppression of the reaction to codeine injection. In two patients the response was completely obliterated, in two it was limited to a 3 cm. area of erythema without wheals or pruritus, and in two the area of erythema and wheal formation was reduced to one-quarter of the control size. One of the latter cases developed slight pruritus at the injection site. The marked reaction to the subcutaneous injection of codeine and the suppression of this reaction corroborates the clinical observation that cyproheptadine blocks the effects of local histamine release in this group of patients.

Discussion

The demonstration of increased histamine in the blood and urine of patients with myeloproliferative disease, the correlation of these elevations with the occurrence of certain physiologic phenomena and symptoms identical to those produced by histamine, the relief from these symptoms afforded by the administration of a potent histamine antagonist, and the lowering of histamine levels after treatment with myelosuppressive therapy all suggest that histamine may play a role in the pathophysiology of myeloproliferative disease.

In the normal subject the cells richest in histamine are the mast cells and
the basophils. Histamine is formed by these cells from histidine by the action of histidine decarboxylase. Upon release from the sites of formation, histamine is degraded by oxidative deamination or methylation and excreted in the urine as imidazole acetic acid, 1,4 methylimidazole acetic acid or their ribosides. Normally, only a small amount of free histamine appears in the urine.

One group of diseases, systemic mastocytosis and urticaria pigmentosa, has already been recognized in which the proliferation of a population of cells (the mast cells) capable of producing histamine results in an increased elaboration of histamine with increased urine histamine levels and symptoms that resemble the known pharmacologic effects of circulating histamine. One may assume that increased urine histamine and histamine-related symptoms would occur in diseases in which proliferation of another population of cells known to be a source of histamine (i.e., the basophils) occurs. It is thus possible that in active, untreated polycythemia vera and "spent" polycythemia with myeloid metaplasia, cells rich in histidine decarboxylase occur as part of the active proliferative process. These cells, containing histamine, circulate in the peripheral blood and, in response to certain stimuli, release their histamine. The released histamine becomes pharmacologically active and stimulates receptor sites that are sensitive to histamine, such as the nerve fibers that mediate itching and the parietal cells of the gastric mucosa. The appearance of increased amounts of histamine in the urine may be explained either by an overwhelming of the normal degradative pathways for histamine or by local release of histamine as the cells circulate through the kidney.

Increased levels of whole blood and white cell histamine have also been found in chronic myelogenous leukemia, another disease in which granulocytic hyperplasia is present. Pruritus, gastrointestinal symptoms and urticaria rarely occur in chronic myelogenous leukemia; occasionally following the institution of busulfan or demecolcin therapy at a time when large numbers of myeloid cells are being destroyed, symptoms resembling the effects of hyperhistaminemia occur. The more frequent occurrence of such symptoms in myeloproliferative diseases as compared with chronic myelogenous leukemia may be due to differences in the binding of histamine within the cell, the rate of release from the cell, or differing local factors that play a role in histamine release. Further investigation of the characteristics of histamine release and the changes in plasma histamine levels that occur in these two groups of diseases in response to certain stimuli is currently underway.

The cells responsible for the elevated blood histamine in myeloproliferative disease have been shown to be present in the white cell fraction of the circulating blood. Previous work has shown that about one-half of the histamine of normal blood resides in the basophil, and in chronic myelogenous leukemia a positive correlation was found between the histamine content of the granulocytes and the percentage of basophils. The basophil has been implicated in histamine formation in chronic myelogenous leukemia by Hartman, who demonstrated a high histidine decarboxylase content of the buffy coat and by Lindell et al. who showed that the in vitro formation of histamine by blood was proportional to the number of mature basophils present. In the
series of patients with myeloproliferative disease presented here, elevated histamine levels and elevated basophil counts occurred in the same subgroups (Tables 1 and 2), suggesting some relationship between these two findings. However, there is not complete linearity between the basophil count of the blood and its content of histamine (Table 3). Two criticisms can be leveled at work that attempts to correlate the number of basophils with either histamine content or the degree of histamine production. The first is that since pure preparations of basophils are not available, all tests and measurements have been performed in the presence of other granulocytes. Although the basophils may normally be the main source of histamine, no assessment of the histidine decarboxylase activity of the other granulocytes in abnormal states such as myeloproliferative disease has been made. The second is that the identification of basophils is based not on the staining of histamine, but on the staining of metachromatic material that is also present in the cell. Thus, a cell may stain as a basophil, but have a low histamine content. The use of a specific histamine stain for the localization of this material in the granulocytes is currently being investigated by the authors.

It should be noted that although the mean basophil count in uncontrolled polycythemia vera was higher than in “spent” polycythemia vera, myeloid metaplasia and myelofibrosis, the mean blood and urine histamine levels were higher in the latter group (Tables 1 and 2). This suggests that either the histamine content of the basophils in these two groups varies or that some other leukocyte also contains histidine decarboxylase and is capable of forming histamine.

The observations that the highest blood and urine histamine levels tend to occur in patients who have the greatest degree of myeloid metaplasia and that a reduction in histamine levels accompanies the shrinkage of liver and spleen produced by chemotherapy suggest that cells formed at the sites of extramedullary hematopoiesis may participate in histamine production. In myeloid metaplasia there is a reversion to an embryonic pattern of active proliferation in extramedullary sites. The occurrence of increased histamine-forming capacity in association with rapidly proliferating tissue and with growth of fetal tissue has been described in several species. In embryonic rat liver the histidine decarboxylase activity has been shown to parallel the histamine-forming capacity and the time course of this activity coincides approximately with that of high hematopoietic activity. Further studies are necessary to elucidate the relationship of rapidly proliferating marrow and extramedullary tissue to histamine elaboration. The recent work of Scott suggesting that increased histamine levels may be more than a consequence of neoplastic tissue growth, and that they may actually be instrumental in stimulating growth, perhaps by virtue of the ability to increase blood supply, raises the hope that as effective histidine decarboxylase blockers become available they may have some place in the therapeutic armamentarium for controlling the proliferation that occurs in this group of diseases.

The demonstration of increased histamine levels in myeloproliferative disease provides a clue to the understanding of some heretofore unexplained...
aspects of its clinical picture and pathophysiology. An awareness of the possible role of histamine in the pruritus that occurs in myeloproliferative disease has led to the successful use of the histamine antagonist, cyproheptadine, for relief of this troublesome and sometimes incapacitating symptom.

SUMMARY

1. Whole blood histamine content was measured in 80 patients with myeloproliferative disease. Increased levels were found in 60 per cent of patients with uncontrolled polycythemia vera, in 7 per cent of patients with polycythemia vera being controlled by myelosuppressive therapy, and in 71 per cent of a group with “spent” polycythemia, myeloid metaplasia and myelofibrosis.

2. The excretion of histamine in the urine was measured in 60 patients, 30 with elevated blood histamine and 30 with normal blood histamine. The urine findings paralleled the blood findings in 90 per cent of the cases.

3. Measurements of cell-poor and cell-rich fractions of blood showed that the histamine is contained in the white cell fraction. Elevated basophil counts were present in 50 per cent of the patients and occurred with the greatest frequency in the groups with elevated blood and urine histamine. A rough correlation between the basophil count and the histamine content of blood and white cell fractions was observed in normal subjects and most cases with myeloproliferative disease. Data obtained in some cases of myeloproliferative disease suggest that the histamine content of the basophil may be abnormal and that other granulocytes may contribute to the total leukocyte histamine.

4. Myelosuppressive agents produced a reduction in histamine (expressed per 10⁶ myeloid cells) and a decrease in urine histamine as control of the myeloproliferative process was achieved. Treatment with phlebotomy alone produced no change in histamine levels.

5. The incidence of pruritus, upper gastrointestinal distress and urticarial manifestations was increased 7-fold, 4-fold and 12-fold, respectively, in patients with elevated histamine levels as compared with those who had normal histamine levels.

6. Cyproheptadine, a potent antihistaminic, successfully controlled pruritus, relieved pyrosis and suppressed urticarial eruptions in patients with elevated histamine levels. Suppression of the reaction to subcutaneously administered codeine (a histamine-releaser) afforded objective evidence that cyproheptadine blocked the effects of histamine release in vivo.

7. The metabolism of histamine and the role of elevated histamine levels in the clinical manifestations and pathophysiology of myeloproliferative disease are discussed.

SUMMARIO IN INTERLINGUA

1. Le contento de histamina in sanguine total esseva mesurate in 80 patientes con morbo myeloproliferative. Nivellos supranormal esseva trovate in 60 pro cento del patientes con non-compensate polycythemia ver, in 7 pro cento del patientes con polycythemia ver regulate per therapia myelosuppressive, e in
71 pro cento de un gruppo de patientes con polycythemia “exhaurite,” cor. metaplasia myeloide, e myelofibrosis.

2. Le excretion urinari de histamina esseva mesurate in 60 patientes, 30 con elevate nivellos sanguinee de histamina e 30 con normal nivellos sanguinee de histamina. Le valores urinari esseva parallel al valores sanguinee in 90 pro cento del casos.

3. Mesurationes in fractiones de sanguine a alte e a basse contento cellular monstrava que le histamina es continite in le fraction leucocytic. Elevate numerations basophilic esseva presente in 50 pro cento del patientes e occurreva con le plus grande frequentia in le gruppus con elevate valores sanguinee e urinari de histamina. Un grossier correlation inter le numeration basophilic e le contento de histamina del sanguine e del fractiones leucocytic esseva notate in subjectos normal e le majoritate del patientes con morbo myeloproliferative. Datos obtenite in certe casos de morbo myeloproliferative suggestiona que le contento de histamina del basophilos pote esser anormal e que altere granulocytes pote contribuer al total leucocytic de histamina.

4. Agentes myelosuppressive produceva un reduction del concentration de histamina (exprimite pro $10^9$ cellulas myeloide) e un declino in le histamina urinari in tanto que un regulation del processo myeloproliferative esseva effectuate. Tractamento con phlebotomia sol produceva nulle alteration in le nivellos de histamina.

5. Le incidentia de prurito, de disconforto gastrointestinal, e de manifestationes urticarial esseva augmentate septuplemente, quadruplemente, e duodecuplemente (respectivemente) in patientes con elevate nivellos de histamina in comparation con patientes con normal nivellos de histamina.

6. Cyproheptadina, un potente agente antihistaminic, maestrava a bon successo le prurito, alleviava le pyrosis, e suprimeva le eruptiones urticarial in patientes con elevate nivellos de histamina. Le suppression del reaction a subcutaneemente administrate codeina (que es un liberator de histamina) forniva evidentia objective a indicar que cyproheptadina blocava le effectos del liberacion de histamina in vivo.

7. Le metabolismo de histamina e le rolo de elevate nivellos de histamina in le manifestationes clinice e le pathophysiology de morbo myeloproliferative es commentate.

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REFERENCES


18. Personal observation.


A Study of Histamine in Myeloproliferative Disease

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