Leukokinetic Studies. VII. Morphology of the Bone Marrow and Blood of Dogs Given Vinblastine Sulfate

By Dane R. Boggs, John W. Athens, Otto P. Haab, Pasquale A. Cancilla, Spencer O. Raab, George E. Cartwright and Maxwell M. Wintrobe

This study is one of a series designed to more clearly delineate the kinetics of neutrophilic granulocytes. In the normal steady state, neutrophils are produced in the bone marrow. Neutrophil production is the result of mitosis of precursor cells and of maturation of the progeny of these cells. In addition to the maturing post-mitotic cells, the marrow contains large numbers of apparently mature segmented neutrophils which have been regarded as a reserve supply of cells available upon demand. Thus, marrow neutrophilic granulocytes can be compartmentalized into two large pools: a mitotic pool, and a post-mitotic maturation and storage pool with cells flowing from the first to the second and then to the blood.

Selective eradication of the mitotic pool would remove the source of supply of cells to the post-mitotic marrow pool and thus permit measurement of its size by assessing the time required for its depletion, reflected by severe granulocytopenia in the blood. The present report deals with a study of the effect of vinblastine sulfate (VLB) on the bone marrow and blood of dogs, carried out with the object of determining whether VLB is capable of eradicating the marrow mitotic pool.

Vinblastine sulfate, an alkaloid from Vinca rosea Linn, has stathmokinetic, antitumor, and possible antimetabolite effects. It has been reported to produce a striking decrease in blood leukocyte concentration without appreciably influencing other blood cells and to have minimal non-hematologic effects.

Materials and Methods

Fifty, apparently healthy, mongrel dogs weighing from 9 to 30 Kg. were used for these studies. Each dog was given diethylcarbamazine citrate as anthelminthic therapy, immunized against distemper and observed for at least 10 days before being accepted for the experimental studies.

A saline solution containing 1 mg/ml vinblastine sulfate (supplied by Eli Lilly and Co.) was prepared freshly and injected rapidly into a foreleg vein.

A daily sample of jugular vein blood was drawn from each dog for the first 10 days to 2 weeks after the administration of VLB and thereafter 2-5 times each week for 2 more weeks. The volume of packed red blood cells (VPRC) was determined in a Wintrobe hematocrit tube. Total leukocyte count and a 200 cell differential leukocyte count were done on each blood sample. In addition, a modified Arneth differential granulocyte count
was done on all blood smears from four dogs. One hundred consecutive neutrophilic granulocytes on each smear were classified as to their type and number of nuclear lobes, as follows: cells in which a one-lobed nucleus had an oval configuration were considered to be metamyelocytes; cells in which the nucleus was elongated without any filamentous separation into more than one lobe were classified as juvenile forms; a cell was considered to have more than one lobe when lobes were clearly separated by a filamentous connection.

In 10 dogs a sample of bone marrow was obtained by aspiration biopsy or by open surgical biopsy on the day before VLB was given. Four hours after VLB was given and on the 1st, 2nd, 3rd, 4th, 5th, 6th, 7th, 9th, 11th, 12th and 18th days thereafter, samples of bone marrow were obtained from four to eight of these dogs. Smears from marrow aspirates or imprints from marrow surgical biopsies were stained with Wright's stain and a 200 cell differential count of granulocytic leukocytes was done. To reduce the error introduced by dilution of the marrow sample by blood, differential counts were limited to evident marrow particles or to imprints from biopsies.

Many of these dogs were also given diisopropylfluorophosphate tagged with \(^{32}\)P (DFP\(^{32}\)) as a label for granulocytic cells of the blood and marrow. The results of this labeling will be considered in a later communication. For purposes of interpreting this study, it should be noted that 16 dogs given DFP\(^{32}\) but not given VLB have shown no significant changes in their apparent good health or in their total or differential leukocyte counts during the month following the administration of DFP\(^{32}\).

No medications other than those reported were given to any dogs and no therapy of post-VLB complications was attempted.

**RESULTS**

The effects of a single intravenous injection of VLB will be considered under four headings: in relation of mortality to the doses of VLB, the pathological examination, the changes in cells of the bone marrow and the changes in cells of the blood.

**Relation of Mortality to the Dose of VLB**

Forty-seven dogs were given from 0.2 to 0.5 mg. VLB per Kg. of body weight. All six dogs given 0.3 mg./Kg. or more died. Three of seven dogs given 0.25 mg./Kg. died whereas only nine of 34 dogs given 0.20 mg./Kg. died. Since we were interested in studying the destructive effects of VLB upon the hemopoietic system, the dosage at which no deaths occur was not established.

Seventeen of the 18 dogs that died developed fulminant diarrhea. Anorexia and occasionally vomiting occurred concomitantly with the diarrhea. An infection was the apparent cause of death in one dog which died on day 7 without gastrointestinal signs but with severe leukopenia. Dogs that developed diarrhea did so during the 2nd to 4th days after VLB. If diarrhea developed, the dog usually died during the succeeding 2 days. Thus 10 deaths in dogs with diarrhea occurred on day 2 after VLB, four on day 3, two on day 4 and the last on day 5. Only three dogs which developed a significant degree of diarrhea survived whereas dogs that did not develop diarrhea remained in apparent good health throughout the period of study.

**Pathologic Examination**

Three dogs were sacrificed specifically for careful pathologic study on days 1, 2 and 3 following the injection of 0.3 mg. Kg. of VLB, and a complete
postmortem examination was done on two other dogs which died on day 3 following 0.2 mg./Kg. VLB. Gross pathologic examination was done on other dogs that died. No abnormalities were noted in any organs except the bone marrow and the gastrointestinal tract. Pathologic changes in the gastrointestinal tract were limited to the small and large bowel. The luminal contents were watery and at times bloody. The mucosa was hyperemic without evidence of ulceration.

The microscopic changes in the bowel on the 1st day after VLB consisted of the following. There were frequent mucosal cells in metaphase, many pyknotic nuclei and many epithelial cells with coarse chromatin clumping in enlarged nuclei. Aggregates of neutrophils were present in several crypts. In the dogs sacrificed on day 2 and 3 as well as dogs examined after death from VLB toxicity, the changes were more intense and accompanied by an exudation of varying numbers of neutrophils. No bacteria were demonstrated in sections of these areas stained with Gram's stain.

**Bone Marrow**

Marrow aspirates done 4 hours after VLB showed many cells in metaphase (fig. 1). The marrow was markedly hypocellular 24 hours after VLB and remained so through day 4 (fig. 2). The cellularity of the marrow had re-
Fig. 2.—Bone marrow biopsies. See legend, facing page.
turned to normal by day 6 and remained normal or increased throughout the remainder of the study.

The decrease in total number of cells in the marrow was accompanied by a marked change in the marrow differential count. Within 24 hours after VLB, virtually all potentially proliferating cells of the granulocytic and erythroid series had disappeared (fig. 2). Megakaryocytes could be found throughout the period in which granulocytic and erythroid precursors were virtually absent.

The percentage change in the precursors of neutrophilic granulocytes of the marrow is detailed in figure 3. By day 1 the proportion of cells younger than a metamyelocyte had decreased from the control value of 17 per cent to 3 per cent. Thereafter, proliferating cells returned to the marrow in an orderly progression with myeloblasts reaching a peak on day 4, promyelocytes on day 5 and myelocytes on day 6. The decrease in myeloblasts and promyelocytes on days 1 and 2, their increase on days 5 and 6, and the increase in myelocytes on days 4 and 5 were all significantly different from the control values (p = <.001). It should be noted that since the total number of medullary cells were decreased, a decrease in the proportion of a given cell type indicates a truly profound decrease in its total medullary mass whereas an increase in the proportion of a cell type does not necessarily reflect an increase in its total medullary mass.

The morphologic characteristics of the regenerating granulocytic precursors were not unusual. No aberrancies akin to those seen after x-irradiation were observed.

Blood Cells

The concentration of leukocytes in the blood was profoundly changed in all dogs given VLB. The total leukocyte count did not necessarily reflect these changes since the rates of disappearance from and reappearance in the blood of neutrophils, eosinophils, lymphocytes and monocytes all differed. Each morphologic type of blood leukocyte will be considered separately. Basophils are so rare in dog blood that they will not be considered. In the 25 dogs which survived a single intravenous injection of 0.2 mg/Kg. of VLB, the concentration curve for each type of leukocyte was followed for 4 weeks. The mean curves for surviving dogs that did not develop diarrhea are shown in figure 4. The statistical significance of these changes at various intervals after VLB is shown in table 1.

The blood neutrophil concentration did not change significantly during the first 3 days after VLB but dropped precipitously on day 4 (fig. 4a and table 1, column a). This pattern of a sudden fall on day 4 was quite consistent. Of 26 dogs which developed no signs of gastrointestinal toxicity, 20 showed a precipitous fall on day 4 and in the remainder there was such a fall on either
day 3 or 5. Dogs that developed gastrointestinal signs showed an earlier and more profound decrease in neutrophils (p < .001) (fig. 5). It should be noted, however, that a decrease in neutrophils did not always precede the development of diarrhea, since six dogs died with diarrhea on day 2 and had normal numbers of blood neutrophils at the time of death.

The severity of neutropenia was related to the dose of VLB. The mean minimal neutrophil count was 600 mm$^3$ in dogs which survived 0.25 mg./Kg. as opposed to 1200/mm$^3$ in dogs which survived 0.20 mg./Kg. VLB (p = <.05). The mean control neutrophil count was the same in the two groups.

Recovery from neutropenia was rapid although the rate of recovery was more variable from one dog to another than was the initial fall. Neutrophils had returned to control concentration by day 5 in one dog while they failed to do so until day 10 in three dogs. During recovery the neutrophil count increased beyond the control level, remained high for about 2 weeks and then decreased to control levels 3 weeks after VLB (fig. 4a).
Fig. 4.—The changes in concentration of blood leukocytes following vinblastine sulfate. The values found in untreated animals are indicated by the interrupted lines.

The proportion of lobulated and non-lobulated neutrophils in the blood changed after VLB (fig. 6). The percentage of juvenile and metamyelocyte neutrophils decreased steadily until day 4 and then sharply increased, preceding but paralleling the increase in total blood neutrophil concentration (fig. 6). The percentage of juveniles and metamyelocytes was significantly less than normal at 4 days ($p < .05$) and the percentage at 7 days was significantly greater than normal ($p < .01$). Morphologic aberrancy of mature neutrophils was minimal. The youngest neutrophil seen in the blood was a very rare myelocyte and metamyelocytes never constituted more than 5 per cent of blood granulocytes in any differential count.

The mean concentration of blood eosinophils was not significantly changed on day 1, was somewhat decreased on day 2 and remained at low levels from day 3 through day 6. Eosinophils gradually returned to control levels by day 9, remained at this level for a week and then increased above control levels. This increase was still evident at the time the study was discontinued and at that time three dogs had achieved levels of more than 2000 eosinophils/mm$^3$ of blood (fig. 4b, and table 1, column b).
Table 1.—Statistical Significance of Changes in Concentration of Blood Leukocytes

<table>
<thead>
<tr>
<th>Day after VLB</th>
<th>A Neutrophils</th>
<th>B Eosinophils</th>
<th>C Lymphocytes</th>
<th>D Monocytes</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 Mean</td>
<td>5,600</td>
<td>470</td>
<td>2,930</td>
<td>460</td>
</tr>
<tr>
<td>Standard error</td>
<td>700</td>
<td>80</td>
<td>330</td>
<td>60</td>
</tr>
<tr>
<td>1 Mean</td>
<td>6,100</td>
<td>440</td>
<td>1,210*</td>
<td>230*</td>
</tr>
<tr>
<td>Standard error</td>
<td>780</td>
<td>100</td>
<td>400</td>
<td>40</td>
</tr>
<tr>
<td>2 Mean</td>
<td>6,100</td>
<td>250*</td>
<td>1,550*</td>
<td>120*</td>
</tr>
<tr>
<td>Standard error</td>
<td>690</td>
<td>40</td>
<td>350</td>
<td>50</td>
</tr>
<tr>
<td>3 Mean</td>
<td>4,700</td>
<td>50*</td>
<td>1,370*</td>
<td>60*</td>
</tr>
<tr>
<td>Standard error</td>
<td>430*</td>
<td>10</td>
<td>170</td>
<td>20</td>
</tr>
<tr>
<td>4 Mean</td>
<td>1,800*</td>
<td>20*</td>
<td>1,910*</td>
<td>140*</td>
</tr>
<tr>
<td>Standard error</td>
<td>310</td>
<td>10</td>
<td>320</td>
<td>30</td>
</tr>
<tr>
<td>9 Mean</td>
<td>9,000*</td>
<td>400</td>
<td>3,710*</td>
<td>1,550*</td>
</tr>
<tr>
<td>Standard error</td>
<td>500</td>
<td>70</td>
<td>1,670</td>
<td>320</td>
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<tr>
<td>21 Mean</td>
<td>5,800</td>
<td>790*</td>
<td>2,600</td>
<td>710*</td>
</tr>
<tr>
<td>Standard error</td>
<td>930</td>
<td>110</td>
<td>190</td>
<td>130</td>
</tr>
</tbody>
</table>

*Indicates that the mean value differs significantly from the control mean at the p < .01 level.

Lymphocytes were the first blood cells to decrease in concentration after VLB. Maximal lymphopenia was usually present on day 1. Return to normal numbers was rapid, passing control values at day 5. Lymphocytosis persisted for a week (fig. 4c, and table 1, column c).

Some decrease in monocytes was present by day 1 but minimal numbers usually were not reached until day 2 or 3. Recovery was rapid and a maximal increase above control levels was reached in 7 to 10 days. A slight but significant monocytosis was still present 3 weeks after VLB (fig. 4d, and table 1, column d).

The VPRC decreased from control levels of 52 ml./100 ml. to a mean minimum of 43 ml./100 ml. on day 7. Dogs not given VLB but given DFP and subjected to the daily withdrawal of 25 ml. of blood, as were the dogs in this study, showed a mean fall in VPBC of 5 ml./100 ml.

No major changes in the number of blood platelets were evident from study of the blood smears.

DISCUSSION

The mechanism of action of VLB is not fully understood. Its stathmokinetic effect is recognized and cells in metaphase were easily demonstrable in marrow and bowel after VLB in this study. It has been suggested that VLB has cell poisoning effects other than its antimitotic effect.4

The degree of gastrointestinal toxicity encountered in dogs has not been noted with comparable mg./Kg. doses in man nor was it reported in rodents in preliminary toxicity studies.5 Since the bowel mucosa is one of the most active mitotic tissues it is not surprising that it should be injured by an agent with stathmokinetic and/or antimetabolite properties.

The correlation of the changes in blood neutrophilic leukocytes with those
Fig. 5.—Relationship of blood neutrophil decrease to the development of gastrointestinal toxicity.

in the marrow provides information concerning their kinetics. The interpretation of these changes is based on the simple model shown in figure 7. In this model, neutrophils are represented as being produced in the marrow by mitosis, undergo maturation and are stored in the marrow until released into the blood. In the end they enter the tissues and are destroyed. The basic assumptions upon which this model is constructed are that cells do not return to the marrow from the blood, nor to the blood from the tissues.

The production of neutrophils in the marrow was temporarily eradicated by VLB insofar as could be determined by morphologic study. Post-mitotic cells, were, however, still evident in the marrow and the number of neutrophils in the blood remained normal for 3 days and dropped precipitously on the 4th
day. Therefore the marrow contained enough post-mitotic granulocytes to replace those normally passing out of the blood for 3 to 4 days. These observations are in agreement with the concept of a marrow granulocyte reserve described by Craddock and coworkers\textsuperscript{6} and with its size as estimated by Patt and Maloney.\textsuperscript{7} The blood neutrophils of the dog are replaced, on the average, 3 times each day.\textsuperscript{8} Thus, the size of the dog marrow granulocyte reserve must be of the order of 9 to 12 times the size of the blood pool. If any increase in blood neutrophil turnover occurs in the post-VLB period, then the normal marrow granulocyte reserve must be even larger.

Increased turnover of blood neutrophils may well have occurred in dogs developing gastrointestinal toxicity. In these dogs, large numbers of neutrophils were evident in sections of their inflamed bowel and in such animals the number of blood neutrophils was maintained at a normal level for a shorter period than in dogs without gastrointestinal toxicity (fig. 5).

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**Fig. 6.—Variation in the blood neutrophil lobe count after VLB.** The values found in untreated animals are indicated by the interrupted lines.
The mechanisms by which mature neutrophils are released from the marrow are obscure. Two general patterns of release of cells from the marrow can be suggested. In the first the number of cells released daily would be a function of the number of cells in the marrow such that a certain proportion of cells would be extruded each day. With such a scheme, as the number of cells in the marrow decreased, the number released would also decrease and the number in the blood would decline gradually. Our data are incompatible with this hypothesis, for normal numbers of blood neutrophils were maintained for 3 days and a precipitous fall occurred on the 4th day. One might also postulate that a certain number of cells is released each day, depending not upon the number of cells in the marrow but upon the number lost from the blood. This hypothesis is compatible with our data. In dogs with inflamed bowels an increased rate of loss of blood neutrophils appears to have accelerated the depletion of marrow stores.

The post-mitotic marrow pool is a maturation as well as a storage pool. Control studies of the marrow revealed 10 per cent segmented neutrophils, 39 per cent juvenile forms and 34 per cent metamyelocytes, or, in terms of the postmitotic pool, the percentages were 12, 47 and 41, respectively. Values for blood neutrophils were, however, 57 per cent segmented, 41 per cent juveniles and 2 per cent metamyelocytes. Thus, it is apparent that cells are not released in random fashion from the marrow post-mitotic pool but usually mature to some degree before release. However, there must be considerable variation in the degree to which a cell matures before it is released, since otherwise all blood cells would be segmented. When the marrow proliferating pool was eradicated and newly formed cells no longer entered the post-mitotic marrow pool, the proportion of segmented cells in the blood increased (fig. 6).

The loss of proliferating precursors of blood neutrophils from the marrow and of neutrophils from the blood was short-lived. The return of proliferating cells to the marrow was heralded by an increase in the percentage of myeloblasts and was followed in turn by an increase in promyelocytes and myelocytes. The blood neutrophils usually returned to control levels by the 7th or 8th day. At this time juvenile forms rather than segmented neutrophils were the predominant blood neutrophils. Juvenile forms were still reduced in the bone marrow but metamyelocytes were somewhat increased. This suggests that as cells were produced and matured beyond the metamyelocyte stage.
they were released rapidly into the depleted blood pool. It seems that the post-mitotic pool in the marrow was not repleted until after the blood pool had reached normal size.

The foregoing assumes that a segmented cell is older than a juvenile form, an assumption with much precedent and some proof.9

The eosinophil is generally considered to originate in the bone marrow in a manner similar to that of the neutrophil. The blood eosinophils decreased in number more rapidly than did neutrophils. If the kinetic model for eosinophil distribution in the body is similar to that for neutrophils, then its turnover rate in the blood must be greater than that of the neutrophil and/or the marrow eosinophil reserve must be proportionately smaller than the marrow neutrophil reserve.

Kinetic interpretation of the meaning of the changes in concentration of blood lymphocytes or of blood monocytes would be highly conjectural in view of the evidence favoring recirculation of lymphocytes10 and the lack of agreement concerning the origin and fate of monocytes.

Some question might be raised as to whether the eosinopenia, lymphocytopenia and monocytopenia that were observed after VLB might be related to elevated plasma levels of adrenal glucocorticosteroids. Steroid plasma levels were not measured since the pattern of leukocyte response observed here was not that observed after the parenteral administration of steroids to dogs. In dogs to which we have given cortisone or cortisol, these three cell types have decreased rapidly and in parallel, reaching low levels by 4 hours.

Comparison of the blood leukocyte concentration curve observed after VLB with that observed after either x-irradiation or alkylating agents is of interest but presents certain difficulties. The site, mode and severity of marrow damage produced by these marrow toxins may differ from one to another and may be further dependent upon different dosage schedules. For example, a few studies of blood neutrophil or total leukocyte concentration after administration of x-irradiation or alkylating agents have reported a steady level for a few days followed by an abrupt fall11-14 as was observed after VLB (fig. 3). However, in these studies leukopenia was still present 10 days after the drug was given and often for much longer periods, whereas after VLB, all dogs had returned to control levels by 10 days. More commonly, the blood leukocyte concentration curve after x-irradiation or alkylating agents has been reported to decline steadily.15-18 Further differences in the action of marrow toxins are suggested by the following observations. Eradication of mitotic cells in the marrow was rapid and fairly complete but quite transient after VLB, whereas after x-irradiation, eradication of mitotic cells from the marrow is a more gradual process, as is repopulation.5,16 During marrow recovery from x-irradiation, aberrant cell forms are often seen5 and such cells were not evident after VLB. These considerations suggest that patterns of cellular destruction developing after different drugs must be interpreted individually with respect to deductions relative to leukocyte kinetics.

**Summary**

The effect of a single injection of vinblastine sulfate was studied in 50
mongrel dogs. Nine of 34 dogs given 0.2 mg./Kg. of VLB died with gastrointestinal toxicity and the mortality rate increased as the dosage of VLB was increased. The morphologic pattern of leukocyte suppression and recovery in the bone marrow and blood was studied in detail in surviving animals.

The cells of the bone marrow were markedly affected by VLB. Within 4 hours there was an increase in the number of cells in metaphase and, by day 1, virtually all proliferating leukocytes and erythrocytes had disappeared. An orderly repopulation of the bone marrow followed.

The neutrophils, eosinophils, lymphocytes and monocytes of the blood were all markedly altered in concentration after VLB. Each type of cell first decreased to abnormally small numbers and then increased to abnormally large numbers in the blood. The curve of disappearance from and reappearance in the blood differed for each cell type.

The changes in blood neutrophil number and morphology were correlated with changes in the blood neutrophil precursor cells of the marrow. The following conclusions were reached concerning the neutrophils and the assumptions implicit to these conclusions were detailed.

1. In the dog, the marrow contains enough post-mitotic granulocytes to replace those lost from the blood for at least 3 to 4 days.
2. The release of mature neutrophils from the bone marrow is a function of the rate at which blood neutrophils are lost and proceeds normally even when the marrow granulocyte reserve is partially depleted.

**Summario in Interlingua**

Le effecto de un injection solitari de sulfato de vinblastina (VLB) eseva studiate in 50 canes hybrida. Novem de 34 canes tractate con 0,2 mg de VLB per kg de peso corporee moriva con toxicitate gastrointestinal, e le mortali-tate cresceva con le augmento del dose de VLB. In le superviventes, le aspectos morphologic del suppression e restablimento leucocytic in le medulla ossee e in le sanguine esseva studiate in detalio.

Le cellulas del medulla ossee esseva afficite marcatemente per VLB. Intra 4 horas, un augmento esseva notate in le numero del cellulas in metaphase. Intra 1 die, practicamente omne le leucocytos e erythrocytos proliferante habeva disparite. Un systematic repopulation del medulla ossee sequeva.

Le neutrophilos, eosinophilos, lymphocytos, e monocytes del sanguine esseva omnes marcatemente alterate in lor concentration post VLB. Omne typo individual de cellula primo declinava a anormalmente basse numeros in le sanguine e montava subsequemente a anormalmente alte numeros. Le curva de disparition e re-apparition in le sanguine differeva inter le diverse typos cellular.

Le alterationes in le numeros e in le morphologia del neutrophilos in le sanguine esseva correlationate con alterationes in le cellulas medullari representante precursors de neutrophilos del sanguine. Le sequente conclusiones esseva derive con respecto al neutrophilos.

1. In le can, le medulla contine satis granulocytos post-mitotic pro re-implaciar illos perdite ab le sanguine durante al minus 3 a 4 dies.
2. Le liberation de matur neutrophilos ab le medulla ossee es un
function del rapiditate con que le neutrophilos del sanguine es perdite. Ille liberation progrede normalmente, mesmo quando le reservas medullari de granulocytos es partialmente depletionate.

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