CHRONIC NEUTROPENIA: FAVORABLE RESPONSE FOLLOWING SPLENECTOMY


The role of the spleen in the pathogenesis of neutropenia has been extensively studied in recent years, and two hypotheses have been advanced. Doan and his associates have observed hyperplasia of the phagocytic reticuloendothelial cells or clasmocytes of the spleen with an abnormal phagocytosis of the granulocytes, and account for the neutropenia on this basis. They have also applied this concept of selective destruction of cellular elements of the blood to explain the anemia and thrombocytopenia which are frequently associated with the neutropenia.

The second hypothesis, which has been strongly supported by Dameshek, is that of "hypersplenism" in which the spleen exerts an abnormal inhibitory effect, probably by means of a hormone, upon the maturation and release of cells from the bone marrow. Dameshek has emphasized this mechanism particularly in idiopathic thrombocytopenic purpura, and also believes that the granulocytopenia which occurs in many types of splenomegaly may be mediated in a similar manner.

A case of chronic neutropenia has been studied and is reported because of the significant elevation of the circulating neutrophils following splenectomy.

CASE REPORT

V. E., a 19 year old white male, was admitted to the hospital on April 10, 1946, with a diagnosis of diabetes mellitus.

The patient's illness began in August, 1945, while aboard ship in the South Pacific, with symptoms of weakness, lassitude, somnolence, polydypsia, pronounced weight loss and muscular cramps in the legs. On September 20, 1945, he had a brief episode of generalized abdominal cramps and vomiting from which he rapidly recovered. A few days later, a second episode occurred and was accompanied by a mild diarrhea. Physical examination at that time was not remarkable, but a blood count revealed leukopenia. Treatment consisted of paregoric and penicillin, and the cramps and the diarrhea ceased. Because of the persistence of the leukopenia, he was transferred to a Fleet Hospital in Manila, P. I. On admission there, a physical examination revealed no significant findings. On November 4, a urinalysis disclosed a 4 plus sugar, and subsequently a glucose tolerance test showed a diabetic curve. The diabetes was controlled by insulin and dietary measures, and the patient was transferred to a Naval Hospital in Hawaii for further study of the leukopenia. On January 16, 1946, a sternal biopsy was performed and revealed no evidence of blood dyscrasia. His course there was uneventful, and, on April 10, 1946, he was sent to this hospital.

The patient had been a lifelong resident of Utah until entry into the Navy in July, 1944. From 1937 to 1944, he had sprayed arsenic of lead insecticide in orchards for three to four day periods several times each summer. For one month prior to the onset of the present illness, he had worked in a paint locker on the ship six hours each day, but, to his knowledge, had not handled any lead paints. From March to September, 1945, he had received atrabin in prophylactic dosage.

From the U. S. Naval Hospital, Oakland, California.

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HARRY A. WEISS AND WILLIAM T. COLLINS

The patient's father, mother, and ten siblings were all living and well. There had been no known occurrence of diabetes or blood dyscrasias in the family.

On admission, the patient had no complaints, and physical examination revealed a well developed, well nourished, young, white male with no positive findings. The urine contained 4 plus sugar and the fasting blood sugar was 315 mg. per cent. The leukocyte count was 2,950 per cu. mm., with 1 per cent bands, 56 per cent segmented forms, and 43 per cent lymphocytes.

The patient was placed on a diet of 2,500 calories and the insulin dosage was regulated at 50 units regular and 30 units of protamine zinc insulin, mixed in the same syringe and given daily before breakfast. Therapeutic agents given in an attempt to correct the leukopenia included the following: pentnucleotide, 10 cc. intramuscularly daily, April 18 to May 13; refined liver extract, 0.1 cc. intramuscularly daily, May 14 to June 1; crude liver extract, 1.0 cc. intramuscularly daily, June 2 to July 1; liver broth, 500 cc. orally daily, May 4 to May 18. None of these agents had any appreciable effect upon the number of neutrophils in the circulating blood.

On May 22, an abscessed tooth was extracted, penicillin being used prophylactically for several days. Two examinations disclosed normal vision and ocular fundi. Neither the spleen or the liver were palpated at repeated examinations of the abdomen. Roentgenograms of the chest and of the flat and long bones revealed no abnormalities. Gastric analysis, using 100 cc. of 7 per cent alcohol as a stimulant, showed no free acid in the fasting, the 30 minute, and the 45 minute specimens, but 16 and 2.0 degrees of free acid were present in the 60 and the 75 minute specimens, respectively. The subcutaneous injection of 0.7 cc. of 1:1000 solution of epinephrine hydrochloride produced a maximum rise in the blood sugar from 64 mg. per cent in the fasting specimen to 22.5 mg. per cent in the 0 minute specimen.

During the last month prior to surgery, the prothrombin time, the bleeding time, and the clotting time were found to be normal.

The patient's course was uneventful until October 1, 1946, when a splenectomy was performed by Capt. Harold F. Young, MC, U. S. Navy. The convalescence was uneventful and the patient was discharged from the Navy on December 14, 1946, because of the diabetes mellitus.

Blood Findings

1. Cellular elements: The erythrocyte and the hemoglobin determinations revealed no appreciable deviation from normal throughout the hospital course. The leukocyte and the neutrophil counts performed in this hospital are shown in figure 1.

On the day of surgery, leukocyte and differential counts at frequent intervals revealed an immediate increase in the number of circulating neutrophils (table 1).

By the afternoon of the first postoperative day, the leukocytes had dropped to 3,850 per cu. mm. and fluctuated only slightly thereafter. On the day of discharge, December 14, 1946, the leukocyte count was
FIG. 1. Blood findings in a case of chronic neutropenia.
5,850, with 63 per cent segmented neutrophils, 33 per cent lymphocytes, 2 per cent eosinophils, and 4 per cent monocytes.

Through the courtesy of Dr. M. M. Wintrobe of Salt Lake City, Utah, where the patient is now residing, the following values were obtained on February 4, 1947: 6,050,000 erythrocytes per cu. mm., 19.0 grams hemoglobin per 100 cc. of blood, 4,500 leukocytes per cu. mm., with a differential of 42 per cent segmented neutrophils, 38 per cent lymphocytes, 6 per cent eosinophils, and 14 per cent monocytes.

2. Mean erythrocyte determinations:

<table>
<thead>
<tr>
<th>Date</th>
<th>RBC</th>
<th>Hb</th>
<th>PCV</th>
<th>MCV</th>
<th>MCH</th>
<th>MCHC</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-21-46</td>
<td>5.08</td>
<td>14.3</td>
<td>53.0%</td>
<td>104</td>
<td>18.5</td>
<td>27.4</td>
</tr>
<tr>
<td>7-18-46</td>
<td>5.20</td>
<td>16.0</td>
<td>52.5</td>
<td>101</td>
<td>30.7</td>
<td>30.4</td>
</tr>
<tr>
<td>9-12-46</td>
<td>4.72</td>
<td>13.5</td>
<td>50.0</td>
<td>106</td>
<td>18.6</td>
<td>27.0</td>
</tr>
<tr>
<td>2-4-47</td>
<td>6.05</td>
<td>19.0</td>
<td>55.2</td>
<td>91</td>
<td>31.0</td>
<td>34.0</td>
</tr>
</tbody>
</table>

3. Platelets: Numerous counts done by the indirect method of Fonio revealed an average concentration of 250,000 per cubic millimeter, both pre- and postoperatively.

4. Erythrocyte fragility: Determination by Sanford's method on two occasions revealed no significant deviation in the fragility of the patient's erythrocytes from that of the control.

5. Cellular response following the injection of adrenalin: This procedure was done five days prior to splenectomy in an effort to determine if the spleen was a significant reservoir of blood. The dosage of adrenalin was 1.0 cc. of a 1:1,000 solution, administered by the subcutaneous route. Blood pressure and pulse were recorded to ascertain the time of maximum response.

<table>
<thead>
<tr>
<th>Time</th>
<th>Pulse</th>
<th>Blood pressure</th>
<th>Leukocytes per cu. mm.</th>
<th>Platelets per cu. mm.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before injection</td>
<td>60</td>
<td>118/65</td>
<td>1.850</td>
<td>200,000</td>
</tr>
<tr>
<td>15 minutes after injection</td>
<td>62</td>
<td>112/68</td>
<td>8.100</td>
<td>140,000</td>
</tr>
<tr>
<td>30 minutes after injection</td>
<td>68</td>
<td>135/70</td>
<td>12.100</td>
<td>255,000</td>
</tr>
<tr>
<td>45 minutes after injection</td>
<td>65</td>
<td>115/65</td>
<td>6.300</td>
<td>104,000</td>
</tr>
</tbody>
</table>

The same procedure was repeated approximately one month following splenectomy as a control measure.

<table>
<thead>
<tr>
<th>Time</th>
<th>Pulse</th>
<th>Blood pressure</th>
<th>Leukocytes per cu. mm.</th>
<th>Platelets per cu. mm.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before injection</td>
<td>68</td>
<td>114/64</td>
<td>7.150</td>
<td>170,000</td>
</tr>
<tr>
<td>15 minutes after injection</td>
<td>80</td>
<td>146/66</td>
<td>9.750</td>
<td>240,000</td>
</tr>
<tr>
<td>30 minutes after injection</td>
<td>76</td>
<td>136/55</td>
<td>9.150</td>
<td>300,000</td>
</tr>
<tr>
<td>45 minutes after injection</td>
<td>70</td>
<td>135/56</td>
<td>9.000</td>
<td>340,000</td>
</tr>
</tbody>
</table>

6. Sternal marrow study: Aspiration of the sternal marrow was performed on July 19, 1946, and the findings were as follows: *Myeloblasts 1 per cent; myelocytes and metamyelocytes 19 per cent; neutrophilic band forms 17 per cent; neutrophilic segmented forms 3 per cent; eosinophils 1 per cent; lymphocytes 10 per cent; no pronormoblasts; normoblasts and macronormoblasts 39 per cent. The myeloid: erythroid ratio was 1.3:1. The production of granulocytes appeared to be somewhat decreased. A very few megaloblasts were found in the smears as resting forms or naked nuclei.*

* We gratefully acknowledge the assistance rendered by Dr. Harry Wyckoff, San Francisco, and Commander John S. Shaver, MC, U. S. Navy, in the interpretation of the histology of the bone marrow and the spleen.
CHRONIC NEUTROPENIA AND SPLENECTOMY

Pathology

The spleen weighed 2.82 grams and measured 14 × 9 × 3 centimeters. The capsule was thin and translucent. Sections revealed a slightly congested, firm, reddish-tan pulp in which the Malpighian corpuscles were readily visible.

Microscopic examination: The capsule and trabeculae of the spleen were of normal thickness and consisted of dense connective tissue and a scattering of smooth muscle cells. Histologically, the chief findings consisted of an increase in number and size of the lymphoid follicles, particularly the germinal centers, and a moderate hyperplasia of the reticulo-endothelial elements lining the dilated sinusoids with enlargement of the "splenic" or "Billroth's cords." The pulp was fairly devoid of erythrocytes but contained a moderately increased number of leukocytes of the polymorphonuclear type. The sinusoids were dilated and contained stagnated white blood cells of the granulocytic series. Only an occasional macrophage was found which contained identifiable nuclear fragments of the granulocytic series, and this was considered minimal or within normal limits after comparison with normal splenic tissue from similar age groups. Many of the lining sinusoidal endothelial cells were laden with coarse granular brownish-black pigment, and an occasional degenerated red blood cell. No phagocytized white blood cells were found in these cells. The hyperplastic lymphoid follicles were unevenly distributed throughout the parenchymal tissue, and the sheathed arteries were not remarkable. Impression smears and supravital stains were not made.

Summary and Conclusions

The case of a patient with chronic neutropenia without splenomegaly, but responding favorably to splenectomy is reported. The surgical procedure appeared to be indicated by the following: (1) exclusion of the extrinsic causes of neutropenia; (2) failure of response to the agents commonly employed to stimulate granulopoiesis; (3) demonstration of granulopoiesis in the sternal marrow; (4) increase in the circulating neutrophils following the parenteral administration of epinephrine; (5) the presence of coexisting diabetes with the potential hazard of infection.

The implication of the spleen as the main factor in the causation of the neutropenia in this case seems well established, although the specific mechanism is not apparent. There was no evidence of abnormal phagocytosis in the microscopic examination of the spleen.

Acknowledgment

We wish to express appreciation to Captain Earl F. Evans, Medical Corps, U. S. Navy, for his assistance in the management of this case.

References

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