NEUTROPENIA

By M. M. SUZMAN, M.D., M.R.C.P.

From the Clinic of Professor W. H. Craib, Johannesburg General Hospital, and the Department of Medicine, Witwatersrand Medical School.

Just as the bone marrow in pernicious anaemia fails to form sufficient red blood cells, and in purpura sufficient platelets, so there exist conditions in which the bone marrow fails to form sufficient white blood cells. Although conditions with leucopenia as the outstanding feature are far from uncommon, very little information concerning them is to be found in text books on medicine. I shall therefore treat the subject in a "text book" manner.

Neutropenia occurs in a variety of different conditions which may be classified as follows:

1. **Infective Diseases.**
   - Typhoid, typhus, measles, influenza, mumps, malaria, dengue, etc.

2. **Diseases due to Physical and Chemical Agents.**
   - Radium (alpha rays), X-rays, arsenic, benzene, arsenobenzol preparations.

3. **Blood Diseases such as Leukopenic lymphatic and myeloid leukaemia.** The so-called aleukaemic leukaemias.

4. **Following severe sepsis.**

5. **Idiopathic neutropenia.**

In this paper I shall deal largely with idiopathic neutropenia, and with the neutropenia associated with severe sepsis. From clinical, prognostic and therapeutic points of view, these two types cannot be considered separately, the only difference being that in the idiopathic variety the neutropenia may be demonstrated to have preceded the onset of the septic manifestations by some days or even weeks, whereas in the other group a normal blood picture may be present with a severe infective process before the onset of the neutropenia. It is thus often difficult to state whether the infective lesions are due to the diminished immunity occasioned by the lack of neutrophils, or whether the neutropenia is the result of the septic process acting deleteriously on the bone marrow. In either case the management of the patient is similar.

The association of profound neutropenia with a severe infective-like condition has only recently been universally recognised as a clinical entity. Although isolated cases have been reported from time to time during the past 30 years, it was only in 1922 that Schultz drew attention to this condition, which he named "agranulocytosis." The first reference in the English medical literature, by Kastin, did not appear until 1927. It would seem, therefore, that agranulocytosis, if not a recent disease, is at least a condition only recently recognised.

**Incidence.** Although it was originally considered that agranulocytosis occurs almost exclusively in middle-aged female subjects, it has recently been shown that this is not the case, and that it may occur in patients of almost any age, and of either sex.

The past history as a rule does not reveal anything of significance, except that periodic sore throats may not uncommonly have been a feature.

The onset, usually sudden, may occasionally be preceded by a period during which indefinite symptoms of ill-health may have been present. In a proportion of cases the extraction of teeth has appeared to have precipitated the attack.

The symptoms most usually complained of are malaise, listlessness, weakness, headache, feverishness with perspiration, rigors, chills, vomiting, muscular pains, palpitation, sore throat, mouth and lips, occasionally with
dysphagia, foetid breath, epistaxis, etc. These symptoms are later followed by collapse, exhaustion, mental stupor, and a condition of extreme prostration, occasionally with delirium.

On examination one is usually struck by the extreme prostration, both mental and physical, and by the fact that these patients appear extremely and often critically ill, out of all proportion to the few physical signs. The throat, and often the tongue, mouth and lips, are the seat of an intense septic affection; ulceration with or without white or greyish membranes, necrosis and bleeding are the usual lesions present, and occasionally a scarlatiniform or morbilliform rash, with or without fine desquamation and petechial haemorrhages. The lymph glands may be enlarged, as also the liver and spleen. Pneumonia may be a feature. Fever, always present is usually marked, being between 103 deg. and 105 deg. F.

Laboratory Findings.

The main feature in this disease is the extremely low white blood cell count, the diminution affecting mainly the neutrophils; this neutropenic leucopenia varies in extent, the total count often falls below 1,000 cells per cu. mm., with very few or even a complete absence of neutrophils. Total counts as low as 50 per cu. mm. have been recorded. The red blood cell count is usually only slightly diminished to between 3 and 4 millions per cu. mm. and haemoglobin to 75 per cent. Occasionally one finds a profound anaemia of the aplastic type, with counts of one million and less. The platelets are usually not affected, except in the rare instances of general bone-marrow aplasia, in which these cells together with the red and white blood cells are markedly reduced in number. The sedimentation rate is almost always markedly increased.

Bacteriological investigations of the oropharyngeal lesions reveals the presence of numerous different organisms, the most important being the streptococcus, haemolyticus and viridans, and Vincent’s fusiform spirochaetal organisms. Blood culture in severe cases will not uncommonly reveal the presence of micro-organisms especially streptococci. The organisms found are usually of low toxicity in regard to experimental animals, showing that their pathogenicity in the patient is dependent more on the lowered resistance of the patient than on the increased toxicity of the micro-organisms.

Pathology. The peculiar character of the morbid process of this disease is determined by the fact that neutrophils are absent from the circulating blood. A true inflammatory reaction, therefore, cannot be said to occur, the lesion being more in the nature of a necrosis. There is a lack of development of the protective inflammatory barriers to infection. Haemorrhages are frequent, where necrosis is present. The lesions occur at any site usually harbouring micro-organisms, which, under altered immunity conditions, become pathogenic. Thus, ulceration, necrosis and haemorrhages may be found not only in the mouth, nose and pharynx, but also in the oesophagus, stomach, duodenum, colon, rectum, vagina and uterus. When pneumonia is present it is found that the alveoli are filled with fibrin and red blood cells, but leucocytes are absent; diffuse oedema and haemorrhages are often present, resembling influenzal pneumonia.

There appears to be a generalized hyperplasia of the cells of the reticulo-endothelial system, noticeable chiefly in the liver, spleen and lymph glands.

The bone marrow shows either an almost complete aplasia of the granulopoietic system, or a myeloid hyperplasia. In the aplastic bone marrow the myeloid cells have failed to mature owing to lack of, or to an interference with, the maturation factor. In the hyperplastic type, although maturation has proceeded normally, and the bone-marrow contains abundant granular cells in different stages of development, the cells have failed to enter the blood stream owing to lack of, or interference with, the necessary chemotactic factor.

Differential Diagnosis.

The diagnosis of this disease depends almost entirely on the carrying out of careful total and differential leucocyte counts in patients who exhibit symptoms of mental and physical collapse, especially if accompanied by sore throat or mouth. This disease must be differentiated from other conditions in which oropharyngeal lesions are present, such as diphtheria, acute follicular tonsillitis, Vincent's angina, etc.; in these conditions the leucocyte count is always either normal or elevated, with a preponderance of neutrophils.
Differentiation must always be made from other conditions in which a leucopenia exists. In the infective diseases enumerated in the classification, the count is rarely, if ever, as low as in agranulocytosis, in which it is almost always less than 2,000 per cu. mm. Further clinical and laboratory data will serve to differentiate these conditions and, moreover, the typical oro-pharyngeal lesions will not be present.

When a physical or chemical poison is responsible, such as those enumerated in the classification, a history of exposure to these will be forthcoming, and in addition to a leucopenia, the other blood elements, namely red blood cells and platelets, will be diminished in number.

It is often well-nigh impossible during life to differentiate idiopathic neutropenia from acute leucopenic lymphatic or myeloblastic leukaemia (so called aleukaemic leukaemia), in which the neutrophils may be absent or greatly diminished in a low leucocyte count, and in which severe oro-pharyngeal lesions are often present. As in agranulocytosis the presence of these lesions is dependent on the low neutrophil count. The diagnosis of leukaemia will not only be possible by being able to recognise that the white blood cells are myeloblasts or lymphoblasts, or by carrying out a bone-marrow biopsy, which will reveal a widespread infiltration with myeloblasts, lymphocytes or lymphoblasts. Not infrequently the autopsy findings alone will serve to differentiate acute aleukaemic leukaemia from agranulocytosis.

Prognosis.

Formerly the mortality of this disease was said to approach 100 per cent. As many mild non-fatal cases are now being detected on account of the increasing use of blood counts, the mortality is now considerably less, probably about 70 per cent.

Fulminating cases are rapidly fatal, lasting from two to ten days. Spontaneous recoveries occur in the milder and more prolonged cases. If the total leucocyte count falls below 1,000 cu. mm. very few recoveries occur. Should recovery take place, either spontaneously or as a result of treatment, there is always a tendency to relapse. Patients suffering from frequently recurring attacks have been observed.

The outcome cannot be determined and there is no certain remedy. In cases with myeloid aplasia (this can be ascertained by biopsy of the bone-marrow), the outcome will depend on whether or not maturation will be resumed; if the maturation factor is supplied and provided it proves effective, about five days must elapse before an increase of neutrophils will be noted in the blood stream. In the cases with normal or hyperplastic myeloid tissue (determined by biopsy) the outcome will depend on the resumption of delivery of the cells from the bone-marrow into the circulation under the influence of a chemotactic factor.

Should the supplying of a chemotactic factor in the hyperplastic cases prove effective, an increase in the number of neutrophils in the blood stream will occur almost immediately.

Treatment.

This consists of the employment of a therapeutic agent which will stimulate maturation of the granulocytes and bring about their delivery into the circulating blood stream. There is no certain agent known which will relieve this condition. Several measures have been employed, the most important being blood transfusion, irradiation of the bone-marrow in the long bones, and the administration of a nucleotide preparation.

No significant beneficial effects have been noted after transfusion. In fact it has been shown that transfusion may actually bring about a reduction in the circulating leucocytes, and is therefore considered definitely harmful. The number of neutrophils added to the blood stream by means of a transfusion would be quite negligible compared to the numbers needed.

Irradiation of the long bones in doses calculated to stimulate granulopoiesis, has been claimed to have been beneficial in some cases. Contradictory results, however, have been reported with this form of treatment, due probably to the considerable variation of dosage required by different patients.

The most effective form of treatment so far known and one with the highest proportion of successes, is that of the administration of a pentose nucleotide. It has long been known that the breakdown products of nucleic acid are capable of producing a leucocytosis by increasing the rate of delivery of leucocytes
from the bone marrow into the blood stream. It appears, too, that nucleotide may act on the bone marrow, not only as a chemotactic factor, for it has been shown to be effective in neutropenia with an aplastic myeloid system. When aplasia is present, the nucleotide is not effective for about five days, this being the time necessary for the maturation of myeloblasts into granulocytes. Should the myeloid tissue be hyperplastic, however, the administration of nucleotide will produce an increase in the circulating granulocytes within one or two days. In the event of this preparation being effective, the blood picture usually returns to normal within a further 5 to 10 days. The nucleotide is administered intramuscularly in doses of 10 c.c.s., twice daily for 5 days, and thereafter once daily until definite improvement has occurred. With the reappearance of neutrophils in the blood stream, the ulcerative lesions of the mouth, throat and lips clear up promptly. This proves that these lesions developed on account of the lack of immunity consequent on the absence of neutrophile leucocytes from the blood. It is of interest also that after the neutrophils have re-appeared, abscesses tend to form at different sites in the body, which later often require surgical drainage. This phenomenon is due to the fact that during the height of the illness, although micro-organisms have entered the blood stream and have been deposited at different sites in the body, pus formation was impossible as the necessary leucocytes were absent, on their re-appearance suppuration thenceforth develops.

Recovery rates approaching 75 per cent, have been reported with this form of treatment in a large series of cases. In fact, this is the method of choice in the modern treatment of agranulocytosis.

It should be understood, however, that occasion to use such treatment can only be realised if the appropriate and timely use be made of the blood pipette and counting chamber.

CASES.

Case 1.

E. M., age 16, male, scholar, was admitted to hospital on the 5th September, 1933, in a state of extreme prostration. The patient was unable to give a history, and the following facts were obtained from his mother.

Five weeks previously the patient had been confined to bed for 8 days with stiffness in the shoulders, elbows and knees, and was treated by his physician for "rheumatics." He recovered but was slightly emaciated. Three weeks prior to admission he developed a rash over his whole body. As far as is known he did not run a temperature during this period, and the rash practically cleared up within a few days. Seven days previous to his admission the patient felt generally "out of sorts" and took to his bed with a high temperature. His condition gradually became graver and on the 4th of September he bled twice from the nose, and is stated to have become "light-headed." He had a cough for several days.

Since the onset of his illness diarrhoea has alternated with constipation (no blood or mucus), and his appetite has been poor.

On examination the patient presented a picture of grave illness. He was lethargic and somewhat delirious. The tongue was furred and dirty; the breath foul, the mouth was ulcerated and bleeding, the pharynx was thickly coated with bloody mucus and appeared acutely injected. Scattered rhonchi were heard all over the lungs; the chest and inner sides of the arms were covered with a punctate erythematous rash. The abdomen was slightly distended; typhoid-like spots were distributed over it which blanched on pressure; the abdomen was soft to palpation and on percussion yielded a tympanitic note. Reflexes were present and normal. Temperature 100 deg. F. Pulse 96 min. Respiration 24 min. Specimen of blood and cerebrospinal fluid were sent for laboratory investigation and the reports yielded the following information:


The C.S. fluid showed numerous erythrocytes, but yielded no pathogenic bacteria on culture.

Blood Count.

<table>
<thead>
<tr>
<th>Component</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin</td>
<td>62%</td>
</tr>
<tr>
<td>Colour Index</td>
<td>0.99</td>
</tr>
<tr>
<td>Red Cells per cu. mm</td>
<td>3,530,000</td>
</tr>
<tr>
<td>Leucocytes per cu. mm</td>
<td>1,800</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>37.5%</td>
</tr>
<tr>
<td>Monoocytes</td>
<td>0.5%</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>61.5%</td>
</tr>
<tr>
<td>Eosinophils</td>
<td></td>
</tr>
<tr>
<td>Mast cells</td>
<td>4.5%</td>
</tr>
</tbody>
</table>
The cells showed anisocytosis and achromia. A provisional diagnosis of typhoid fever had been made on admission, and the patient placed on a milk and meat extract diet with copious fluids. Pituitrin was administered frequently on account of the extreme prostration.

Two days after admission a definite diagnosis of agranulocytosis was made and nucleotide (10 c.c.s. twice daily intramuscularly) treatment was commenced. The patient’s condition rapidly became worse, and terminated fatally at 5 a.m. on the 12th September, six days after admission, and on the 4th day of nucleotide therapy.

Below is given a chart of progress:

<table>
<thead>
<tr>
<th>Date</th>
<th>Temperature</th>
<th>Pulse Rate</th>
<th>Respirations</th>
<th>R.B.C.</th>
<th>Polys.</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sept. 6</td>
<td>101.2—98.4</td>
<td>108-100</td>
<td>40-28</td>
<td>3.5</td>
<td>2,500</td>
<td>32.0 800</td>
</tr>
<tr>
<td>Sept. 7</td>
<td>98—101</td>
<td>84-120</td>
<td>24-36</td>
<td>3.3</td>
<td>1,230</td>
<td>12.0 144</td>
</tr>
<tr>
<td>Sept. 8</td>
<td>103—102</td>
<td>104-120</td>
<td>32-40</td>
<td>3.4</td>
<td>1,400</td>
<td>3.0 42</td>
</tr>
<tr>
<td>Sept. 9</td>
<td>100—105.5</td>
<td>100-108</td>
<td>28-30</td>
<td>1,100</td>
<td>0 0</td>
<td>0 0</td>
</tr>
<tr>
<td>Sept. 10</td>
<td>105.4—106</td>
<td>116-132</td>
<td>40-44</td>
<td>3.1</td>
<td>830</td>
<td>0 0</td>
</tr>
<tr>
<td>Sept. 11</td>
<td>104.5—105.5</td>
<td>120-152</td>
<td>40-48</td>
<td>3.1</td>
<td>830</td>
<td>0 0</td>
</tr>
<tr>
<td>Sept. 12</td>
<td>died 5 a.m.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CASE 2.

A. G. W., aged 44. Occupation, Clerk.
Admitted to the General Hospital 21/9/33 with the following history:—

A feeling of general malaise, headaches, and pain in the back for the last five weeks, which the patient ascribed to "flu." Three weeks ago he noticed a yellow colouration of the eyes, and his throat which had been sore for a week or two became progressively more painful. He was becoming weaker and weaker, and eventually sought medical aid on the 20th September, 1933.

On admission his condition as described in the physician’s notes, was as follows:—

Malnourished adult, male subject, appearing extremely ill. Evidence of slight recent loss of weight. There was a yellowish tinge in sclerotics. Teeth were absent. Throat was injected, with ulceration of right pillar of the fauces. The tongue was furred and dry. The chest was clear. There was some distension of the abdomen with diffuse tenderness. The spleen and liver were not felt. Nothing abnormal was detected in the central nervous system. Temperature 101.6 deg. F. Pulse 136. Urine showed nothing abnormal.

Clinically the patient appeared to be suffering from typhoid fever. His temperature was of the continuous type and remained high for the whole duration of his illness, the pulse keeping pace.

A blood count taken soon after admission revealed a remarkable leucopenia with neutropenia, and a fairly well marked secondary anaemia. The blood findings were as follows:—

Red Blood cells … 3,590,000 per cu. mm.
Haemoglobin ….. 52%
Colour Index ….. 0.79
Leucocytes ….. 400 per cu. mm.

Differential Count.

Polymorphonuclears …………. 5.5%
Large mononuclears …………. —
Lymphocytes …………. 98.5%
Eosinphils …………. 1.0%

A diagnosis of agranulocytic angina was made, and nucleotide being unavailable he was given deep therapy to the long bones every other day.

No significant change occurred in the blood picture, the total leucocyte count on the following day being 500 per cu. mm. of which 8 per cent. were neutrophils and 97 per cent. were lymphocytes. The patient became progressively worse, the leucocytes almost disappearing from the blood stream. Coma and incontinence of urine supervened, and he died nine days after admission.