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## General and hematological considerations in neutropenia

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GENERAL AND HEMATOLOGICAL CONSIDERATIONS IN  
NEUTROPENIA

by

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Submitted in Partial Fulfillment  
of the Requirements for the Degree  
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## INTRODUCTION

During the past fifty years our knowledge of the diseases of the blood has advanced remarkably, but this advance has been made chiefly in diagnosis and classification. At the present time there is much theory and almost no real understanding of either the normal or the pathological physiology of the hemopoietic tissues and this lack of the most fundamental facts has led to elaborate confusion in the nomenclature and classification of the blood diseases. Neutropenia is at present one of the most discussed and least understood conditions and it is my aim to contribute something which will throw light on its primary etiology and mechanism.

Schultz, in 1922, called attention to four cases of an acute febrile disease in which there were necrotizing lesions in the throat, extreme prostration, mild jaundice, leukopenia with almost complete absence of granulocytes, and invariable fatality. (Taussig 1931) On further study of the literature one finds that cases of fatal pharyngitis had been described by Gubler in 1857, by Mackenzie and Morell and by Senator in 1880, by Brown in 1902, and by Turk in 1907 (Pepper 1931). Brown and Turk were the only ones in this group to make note of the lack of granulocytes in the blood of their

patients and Brown presented a very complete case history in which he called attention to the leukopenia, to the lack of pus at the site of the pharyngeal lesion, and to the fact that uric acid and purine bases were distinctly increased in the urine.

Since Schultz focused attention on this disease in 1922 over five hundred cases have been reported in the literature and a study of many of them has resulted in the following definition by Beck (1933 a):-  
"It is a grave disease of unknown etiology with marked reduction in the white blood count, especially in granulocytes, and accompanied by aplastic, normal, or hyperplastic myeloid tissue. Following the neutropenia there may be any number of secondary lesions and symptoms, acute or chronic."

The original term, "Agranulocytic Angina " given by Schultz, is considered by many workers to be a misnomer because (1) about one-half of the cases do not show angina early in the disease and it is therefore believed to be a secondary manifestation; and (2) "agranulocytosis" suggests a condition in which abnormal neutrophiles, without granulations, are found in excess numbers in the circulating blood, whereas in this disease the individual cells are entirely normal and their number is decreased. Schilling (1929) suggests the term "Malignant Neutropenia " as being more exact.

Baldrige and Needles (1931) prefer "Idiopathic Neutropenia", and David uses " Sepsis with Granulocytopenia".

Because " Neutropenia " is both brief and accurate it will be used in this paper and whenever necessary it will be qualified by the words "benign" and "malignant" as is done by Beck.

### OCCURRENCE

Cases of Neutropenia have been reported in both males and females of all ages from six months to seventy-two years but a large percentage have been in middle-aged women. There is no seasonal incidence of this disease and it seems to be most prevalent where the climate is varied. Germany and the United States have reported the greatest numbers of cases but this apparent geographical distribution may be only the result of exceptionally careful diagnosis in these countries. Furthermore, neutropenia has been found in all classes of society though it is more frequent in the leisured group and among members of the white race. Its occurrence among doctors and nurses in rather a high percentage is probably a reflection of good medical attention.

The fact that seventy-five percent of the cases have been reported in women between forty and sixty years of age led Roberts and Kracke (1930) to make

a careful study of the case records of all women between these ages who had come to their clinic over a ten year period. Over eight thousand records were reviewed and the blood counts classified in the normal and neutropenic groups. Interpretation of these counts was based on a white blood cell number of six thousand with sixty-seven percent of neutrophiles as the low normal. On this basis one out of four patients showed a mild granulocytopenia and about nine hundred had leucocyte counts below three thousand. Just what bearing these findings have on the actual incidence of the acute disease known as Neutropenia is so far doubtful as cases of the fulminating type have not arisen in this group and therefore the relation between habitually low white cell counts and acute neutropenia is not known. Doan (1922) mentioned that persons with habitually low counts have bone-marrow capable of minimal response only, so that insufficiency is always imminent. On the other hand the fact that a given patient may be known to have reacted to a previous infection with a leucocytosis suggests that there is not a permanent marrow defect. (Chrisman and Hinton 1931).

More specific factors which have been considered to be significant in the etiology of Neutropenia are benzene, arsphenamine, barbitals, and the

X-ray. It is known that depression of the granulopoietic centers may follow any of these agents but the cases observed have not been entirely typical of Neutropenia. Schultz considered that there was some specific infection and that the leukopenia was secondary, but the more recent articles state that the infection is secondary in all cases. However, some experimental work by Dennis in the last year may be reopening the question. A congenital anomaly of the bone-marrow, allergy,<sup>and</sup> nervous paralysis of the hemopoietic tissues have all been mentioned but there is little evidence that any of these are important. The presence of some endogenous disturbance of the marrow is now considered to be the really important factor, but up to the present time its nature is not understood.

#### CLINICAL SYMPTOMS AND FINDINGS

The onset in most cases is quite sudden, and usually there is no previous medical history of any importance. Weakness, lassitude, and fever are marked from the first in all cases. Chill, headache, nausea, ~~sore~~ sore throat, cough, and even delirium have been known to usher in an attack. The fever varies between 101 and 106 degrees and is of the continued rather than the septic type. Sore throats are more frequent and



more severe in those persons who have poor oral hygiene, and are apt to be accompanied by enlargement of the regional lymph glands. The extreme degree of prostration continues throughout the illness and is frequently the only subjective symptom, although sore throat, rectal distress, or gastro-intestinal uneasiness may be noted. A very fetid odor to the breath is suggestive of the presence of a gangrenous lesion in the oral cavity.

The general physical examination seldom reveals much of importance. A moderate fever and pulse elevation in a patient who seems sicker and more toxic than would be expected from the physical findings should always call for a study of the blood, and a marked lowering in the white cell count with reduction of neutrophilic elements in an otherwise normal blood picture is sufficient to suggest the possibility of Neutropenia. Enlargement of the lymph nodes is not constant but is found only in those cases showing local lesions and is secondary to infection.

The local necrotizing lesions are the specific physical manifestations which should always be looked for carefully when there is any question as to diagnosis. The lesion usually seen is a pit-like ulcer having a gray base and overhanging margins, and surrounded by

a zone of induration. Early in some cases the ulcer is covered by a white or yellowish exudate which later sloughs off. Costen (1933) considers that the real point of infection is at the gum margin or on the tonsil and that there is an undermining of the surface to a spot one-half to one centimeter distant, where the lesion may be seen. A swollen area may be present at this point before the ulcer forms and some physicians have considered it to be an abscess and have incised it, but no pus has ever been obtained from such an area. Hence, it is no longer considered wise to do any operative work as nothing is accomplished by it, and the presence of infection prevents healing of the scar. Similar ulcers have been reported in the nose, mouth, vagina, rectum and (on autopsy) in all parts of the gastrointestinal and respiratory tracts. The nature of the condition makes it probable that ulcers may occur on any surface where pathogenic micro-organisms are present. Zininger, in a recent issue of the Journal of the American Medical Association (1933) has reported two cases which were unusual in that there was no angina but instead were numerous necrotic lesions of the skin and subcutaneous tissue. The possibility of the skin lesions being an allergic manifestation has been suggested by Gatewood and Baldrige (1927) who have called atten-

tion to the Arthus Phenomenon of local anaphylaxis as a possible explanation of the local gangrene.

The laboratory findings in Neutropenia are not remarkable except for the blood count in which there is a marked leukopenia with a total reduction in the neutrophiles and an absolute decrease in the number of lymphocytes. There is no anemia unless the disease is unusually prolonged and cachexia develops. The platelets have been found to be present in normal numbers even in those cases which show some hemorrhagic tendencies. Biopsies of sternal marrow have been found of value in determining the diagnosis and the prognosis but it seems that such a procedure is not without danger to the patient in view of the lack of resistance to infection and the poor powers of healing. Positive blood cultures have been obtained in many cases and a variety of organisms isolated, but since this is often a late finding it is considered to be the result of a breakdown of the normal resistance. Bacterial studies of the throat and mouth have shown many different organisms but no one kind has been found constantly. The ones most frequently present are the spirillum of Vincent's angina, the streptococcus, the staphylococcus, and the pneumococcus. Urine findings have been neither constant nor significant.

### CLASSIFICATION

As is true in the study of all new diseases, there was first a very definite description of a few cases; then there were reports of similar findings by other physicians; following this came the reporting of conditions which were identical in most particulars but presented slight variations from the established type; and after this the syndrome was broadened to include many diverse conditions and great confusion resulted. After this had happened it became necessary to narrow the concept of the disease and to classify the various types. This has been done as follows;- (1) The acute, fulminating type of Schultz with the typical angina, (2) The acute, fulminating type without local or general evidence of infection or sepsis. (3) A sub-acute type with fever lasting several days, lymph node enlargement and moderate leukopenia, which goes on to complete neutropenia and pharyngitis later, and may terminate in recovery in one to three weeks. (4) There is a chronic type with remissions in which a patient may have two or more attacks within several months before she finally dies. (5) There is the sub-chronic type which has an insidious onset with mild leukopenia. This group of patients may live for years carrying low blood counts, the only symptom being easy fatigue. And (6) two cases have been reported who have had cyclic

recurring attacks over periods of years. These recurring attacks are remarkably regular in the time of their appearance and therefore the suggestion has been made that they are initiated by some endocrine substance. (Kracke 1931 and Rutledge et al. 1930) The diagnosis of all types is made by the neutropenia without anemia and with no absolute increase in the number of lymphocytes in the blood. Therefore, it appears that the laboratory is of more than usual importance in this condition.

#### PATHOLOGY (GENERAL)

The peculiar local lesions found in so many cases of neutropenia are the result of absence of circulating neutrophils and are typical examples of necrosis without granulocytic infiltration. The gastrointestinal tract is the commonest site for such lesions, the main factor being the lack of the usual protective elements in a location where there is gross infection. These ulcers may be found from the oral to the anal orifices and are in all respects similar. Also, multiple hemorrhages may be seen in the mucosa and suggest that infected emboli may be an important factor in initiating the tissue necrosis (Hueper 1930). The lesions themselves are gangrenous areas covered by a dirty

coat and surrounded by a dark red zone of induration. Edema may be marked.

The bone-marrow changes are of two types, aplastic and hyperplastic, and there may be the appearance of liquefaction of the marrow. This tissue will be discussed in detail later in this paper.

The condition of the spleen is quite variable but in most cases the organ is somewhat enlarged. This may be mainly due to toxicity and edema but the tissue is never soft as in septicemia but is firm and red. (Hueper 1930) Most observers agree that the lymph follicles are reduced, often being very small and atrophic, and that the enlargement of the spleen is due to an increase in the reticulo-endothelial elements.

The liver is usually enlarged by cloudy swelling and fatty degeneration, and there is often an increase in the number of Kupffer cells and lymphocytes. Emboli and infarcts are frequent and there may also be some bile casts in the capillaries. These probably explain the jaundice sometimes seen.

The submaxillary, cervical, peribronchial, and mesenteric lymph nodes are often enlarged and may contain hemorrhages. Frequently there is marked degeneration in those areas which are called germinal centers by many, but which Latta (1922) has demonstrated

to be centers of degeneration. There is frequently an associated general proliferation of the reticular cells. (Beck 1933 a).

The lungs almost always show evidence of bronchial pneumonia in fatal cases, with a marked congestion and little if any evidence of inflammatory cell reaction (Rose and Houser 1929). Frequently there are sub-pleural hemorrhages which may be caused by bacterial emboli.

The kidneys also may show evidences of emboli and there are no signs of the usual type of inflammatory reaction in spite of the fact that numerous bacteria may be present in the urine of the pelvis and tubules. The whole organ shows cloudy swelling with degeneration and necrosis of the epithelium.

In the heart, sub-pericardial and sub-endocardial hemorrhages are frequent. Parenchymatous degeneration may also be found in the muscle and be a factor in hastening the death of the patient.

The external genitalia are probably the most frequent site of local ulceration outside the digestive tract.

#### TREATMENT

The treatment of any disease should, of course, be directed toward the removal of the cause

but in Neutropenia that is impossible because the etiological factor or factors are unknown. It is a fact that conditions closely simulating Neutropenia may be caused by benzene or arsphenamine poisoning and in these recovery is usually prompt as soon as the drug is withdrawn, providing that the patient is not moribund. The confusing similarity of those cases definitely due to poisoning and those which can be traced to no cause whatever has made the treatments used more or less empirical; whenever something new is tried it is hoped that it will succeed not only in benefiting the patient but in suggesting a possible etiological factor in the disease.

All students of the problem of Neutropenia seem to be agreed that there is some arrest in granulopoiesis or in the delivery of cells but what causes this or where to look for the necessary stimulant to bring about recovery is still unknown. It seems probable that remissions are almost always spontaneous when they occur, and that the differences in the percentages of fatal cases under different regimes may be due to faulty diagnosis or to conclusions based on too few cases. As an example of this, Taussig (1931 ) states that he has observed some cases to pass over into acute leukemia, but it seems more likely



that the diagnosis was incorrect and that Taussig was confused by the aleukemic stage of a leukemia.

Treatment directed toward the prevention of Neutropenia is obviously difficult when one does not know what it is that he is preventing. However, it is always wise to direct attention toward the maintenance of good health, to avoid excessive fatigue, to insure adequacy of diet, and to avoid severe mental shocks whenever possible. More specifically, it is evident that benzene derivatives, including the barbitals, should be used sparingly, especially by those persons who habitually carry low white cell counts. The same is true for arsphenamine but the risk of withholding that drug when it is indicated may be so great that the danger of Granulocytopenia must be disregarded except in persons who have had a previous attack of this disease. Surgery should be limited to absolute necessity, especially in leukopenic persons, as a number of cases have been reported in which the onset of Neutropenia followed some surgical interference. Hodges in 1930 noted the frequency with which simple tooth extractions were followed by severe leukopenia, and he calls special attention to the likelihood of the condition being present in those cases in which there is post-operative oozing of blood.

The treatment of the local ulcers is generally considered to be unimportant except to maintain fair asepsis. In contrast, Hamburger ( 1931 ) stated his belief is vigorous local treatment, although even he felt that incision of the area should always be avoided. Beck (1933 b ) advocates the frequent use of a spray of a saturated solution of potassium chlorate. She also suggests swabbing the gums every few hours with a solution of copper sulphate. Turpentine, gentian violet, acriflavine, and many other antiseptics have been used but seem to be without any specific value.

Various general measures based on theoretical considerations have been tried, without conspicuous success, in an effort to discover some specific therapy for Neutropenia. Taussig (1931) and Hare ( 1932 ) both noted allergic tendencies in some patients and the latter had a case in which there was also an upset in the calcium metabolism; therefore he used calcium gluconate and granulocytes reappeared in the blood in five days. As spontaneous recovery occurs at about this time and as Hare's work has not been repeated it is doubtful if this agent is of value. Since Minot and Murphy introduced liver therapy in Pernicious Anemia there has been almost routine use

of some liver substance in all blood diseases. The extract is considered by Beck (1933a) to be entirely without effect in granulopoietic disturbances, and administration of the whole gland has not proved of any real value although there are some cases in which recovery has followed its administration. Kracke (1932) feels that the use of massive doses of liver by mouth can do no harm and in view of the seriousness of the disease should be tried if there is even the faintest possibility of its being of benefit.

Foreign protein therapy was used in an effort to stimulate leukocytosis but has been abandoned. The bad effects of any such stimulation have been mentioned by Dennis (1932). An extract of bone-marrow as well as a leukocytic extract were mentioned by Beck (1933 b) but have not been adopted generally. Splenectomy was found by Johnstone in 1922 to produce temporary leukocytosis and it was therefore tried in one case of Neutropenia but was followed by death. The autopsy showed the marrow to be leukemic (Beck 1933a).

There are three therapeutic procedures which are of theoretical value and have been used extensively with some good results. These procedures are (1) transfusions, (2) radiation, and (3) the administration of nucleotides. Doan (1922) suggested that the nucleo-

tides were the common factor in all of these as the X-ray, in causing destruction of tissue, liberates nucleotides and transfusion carries this same substance to the patient from a healthy donor.

The use of transfusions in many diseases has become popular in the last decade. Their use in neutropenia was advocated by Hamburger in 1931 and by Kracke in 1932 as the most specific therapy known. Most physicians have tried a number of remedies in every case either all at once or in rotation in a sort of panic to do all possible for their patients, and as a result we know very little of the effect of any one procedure. There are probably only a few cases of Neutropenia in which transfusions have not been used at some time and this is probably warranted as a logical method of tiding the patient over until spontaneous remission can occur.

Fisher in 1930 reported a case in which recovery occurred after he had given an immune transfusion and, thus, he feels that this may be the proper line of treatment. In criticism of this work, Beck (1933 a) points out that recovery occurred at the usual time for spontaneous remission, that the tendency to recurrences in all cases is evidence that no immunity is built up, and that the strain put on the donor, who

is himself a candidate for another attack, is not good practice.

Treatment of Neutropenia with small doses of X-ray was first advocated by Friedeman in 1927. He used 1/20 of an erythema dose, applied one to four times over large areas of the body surface. Waters and Firor (1931) reported the irradiation and cure of thirteen out of fifteen cases which were not complicated by sepsis. They observed improvement in the blood within thirty-six hours and feel that the results obtained justify the further use of their method even though the rules of application are not yet completely standardized.

Isaacs in 1932 discussed the effect of roentgen rays on the blood-forming tissues and in his article states that there is no evidence of any toxic necrotic action of X-ray in therapeutic doses. He emphasized the fact that the results of irradiation depend entirely on the stage of development of the cells acted upon; blasts or younger cells are stimulated to rapid reproduction, because that is their potentiality, whereas myelocytes or medium sized lymphocytes are stimulated to continue their normal life history at a more rapid rate and then to be eliminated as normal senile cells. A marked hastening of a large number of

cells toward senility may give the appearance of a depressive action on formation of cells. Isaacs states in conclusion that the aim of X-ray therapy in Neutropenia is to stimulate the division of blast cells without causing too rapid maturing of the cells already present. Beck (1933 a) mentions the possibility of roentgen rays having some effect on the organs of internal secretion and thus bringing about a secondary elaboration of a maturation factor for granulocytes. There is no evidence for this theory at present, but it is a possibility to be considered.

In 1877 Altmann discovered that nucleic acid was present in all cells of the body and was especially plentiful in the liver, spleen, and thymus as those organs have a large proportion of nuclear material. Altmann also observed that administration of nucleic acid caused a marked leukocytosis, preceded by a leukopenia lasting several hours. This work suggested the therapeutic use of nucleic substances to increase the white blood cells and therefore the germicidal power of the blood, but the results did not justify the procedure.

More recent work has substantiated Altmann's findings and various nucleotides have therefore been used therapeutically in granulocytopenic states. Ade-

nine and guanine have been shown not to be followed by any preliminary fall in the number of leucocytes and therefore these latter substances seem to be better suited to the treatment of Neutropenia. Reznikoff (1933) published a series of cases of leukopenia in which he used adenine sulphate and found that definite improvement in the blood picture was often apparent within forty-eight hours. Doan in 1922 gave nucleotides to healthy animals and found that myeloid foci were increased in the bone marrow in five days and thus showed that there was a true chemotactic effect.

Two years ago Jackson and Parker stated that pentose nucleotides were the forms present in normal blood and therefore they chose them for the treatment of Neutropenia; of the twenty cases treated fourteen recovered. These men remarked on the fact that the latent period, before improvement showed in the blood, was the same as that in the liver treatment of Pernicious Anemia and therefore they drew a parallel between the two diseases. The mortality reported by Jackson and Parker was remarkably low ( 33% ) but their cases were carefully selected and not complicated by sepsis. It appears at present that nucleotide therapy is the best we have for use in Neutropenia, but it is still probable that most recoveries are spontaneous

and occur regardless of the medication used.

### PROGNOSIS

The earliest reports of this disease by Schultz and others gave the mortality as practically one hundred percent. In 1931 Reznikoff reviewed most of the cases reported in the literature and placed the figure at eighty-three percent. In the same year Taussig and Schnoebelen gave seventy-five percent as the figure found in 328 cases, and remarked that when X-ray therapy and transfusions were used this was reduced to about sixty percent. It is probable that the somewhat lower mortality reported recently is due to the fact that with routine use of blood counts in diagnosis the milder cases are picked up.

Beck (1933 b) makes the observation that there are apt to be sequellae in recovered cases. Loss of weight and myocardial weakness are the two remarked on by this author. It is also a known fact that few recovered cases are free from the danger of subsequent attacks of Neutropenia which are apt to be fatal.

### HEMATOLOGICAL CONSIDERATIONS

#### General Theoretical and Experimental Work

Since Neumann in 1868 first pointed out that the function of the bone-marrow was the formation of



blood cells, there has been constant controversy concerning the exact mechanism involved. It is agreed that the various myeloid elements develop from a common stem cell, the hemocytoblast, through proliferation and differentiation. It is also agreed that lymphocytes develop in the lymphoid tissue from certain large cells, many of which are morphologically identical with the hemocytoblasts of the marrow. But it is not agreed as to whether the large lymphoid cells of the marrow and lymphoid tissues are fundamentally different and have unlike developmental potencies (dualistic theory) or are identical and that all blood elements arise from the same stem cell (unitarian theory).

The dualists, championed by Sabin, etc., are certain that there are fundamental biological and structural variations in the two stem cells. Up to the present, morphological differences have been found only in dry smears of pathological blood and these variations are minute and subjective. The presence of oxydase granules was thought for a time to differentiate the myeloid from the lymphoid system, but it has been found that under unusual circumstances the granules disappear from the myeloid cells or are elaborated by the lymphoid. A strong argument in favor of the dualistic theory was the fact that variation occurred in the two tissues in certain pathological conditions, but it

has been shown recently that these responses are probably due to the different stimuli given rather than to any fundamental differences in the tissues themselves.

The unitarians, led by Danchakoff, Downey, Jordan, and Maximow consider the lymphocyte as a polyvalent cell which usually does not differentiate into higher types but may do so under special conditions. This group of investigators look for instances of unmistakable erythropoiesis or granulopoiesis, with transitions from typical lymphocytes, in lymphoid tissue following myeloid stimulation, and for extensive lymphogenesis in the bone-marrow. Danchakoff (1915-8) emphasized the common origins of both stem cells in embryonic life. She also states that the adult organism retains a stock of undifferentiated mesenchymal cells which may multiply and differentiate in certain conditions of disturbed equilibrium. Maximow (1924-1930) considers the small lymphocyte to be capable of differentiation into myelocyte, erythroblast, or megakaryocyte. Jordan (1925) goes so far as to suggest that lymphocytes may be normally filtered out of the blood stream into the marrow and there function as mother cells of the myeloid line. Bloom (1926) claims to have observed direct and unmistakable transformation of lymphocytes into granulocytic myelocytes

in the central zone of lymph nodules.

A great deal of experimental work has been done in an effort to determine the potentialities of particular cell types in the hemopoietic organs. It seems important in the problem of Neutropenia to determine as clearly as possible just what these potentialities are, and so to determine what factors modify granulopoiesis. Brown in 1915 found that the injection of toluene caused an initial myelocytic hyperplasia in the marrow but no increase in the number of neutrophiles in the circulation; he therefore concluded that the immature neutrophiles were phagocytosed by giant cells. As far as can be determined Brown's theory has never been proved so that we do not know whether or not there is any possibility of the giant cells being the cause of Neutropenia by their overactivity.

Dominici in 1920-1 injected typhoid bacilli into rabbits and found subsequently a definite extramedullary myelopoiesis in lymph nodes and spleen. This type of work suggested the use of foreign protein therapy in Neutropenia, but the results in disease have not been encouraging.

The most conclusive work done in the effort to prove the unitarian theory of blood formation is that done by Maximow in 1923 in which he found that tissue cultures of isolated lymphoid tissue showed

transformations into all stages of granulocytes. Two years later he studied explants of rabbit blood and found that they behaved as the cells normally do in inflamed tissue after emigration from the blood vessels. The granulocytes gradually degenerated and the lymphocytes and monocytes remained alive and showed progressive development. This work may explain why granulocytes gradually disappear and lymphocytes remain in leukopenic states. It is necessary, however, to consider that the source of all hemopoiesis is cut off.

#### Anatomy and Physiology of the Granulopoietic Tissues

The granulopoietic tissue of the body is located in the red bone-marrow of the ribs, vertebrae, sternum, skull, and long bones. The volume of the bone-marrow in an adult is about fifteen hundred cubic centimeters, or practically equal to that of the liver. From three to twenty times as much of the marrow is occupied with the formation of granulocytes as with the formation of erythrocytes. This latter condition is made necessary by the shorter life of granulocytes in the circulation and by the fact that much of their function may be outside the blood stream, especially in infection.

The microscopic anatomy of the bone-marrow

shows that there is a stroma consisting of undifferentiated cellular syncytium, histiocytes, and fibers, and that all of the myeloid elements in immature or mature form may be found in this tissue. Variable numbers of young cells, in like stages of development, may be found in clusters throughout the organ. According to Isaacs (1930) the immature cells are fixed in a viscid intercellular matrix until they become mature and finally discharge themselves by liquefaction of their surrounding substance, and by migration through the capillary wall into the blood stream.

The factors which control maturation and delivery of blood cells are not definitely known. It is probable that there is a chemotactic agent which is capable of stimulating the discharge of cells and this agent has been considered by a number of hematologists to be a nucleotide, probably derived from the destruction of large numbers of senile leucocytes. In 1924 Jordan and Speidel stated as their opinion that the fundamental stimulus which induced the lymphoid hemocytoblast to differentiate into a granular leukocyte was some product of protein metabolism, and at the present time that is as far as we are able to go in determining the nature of the maturation factor. Sabin's work (1925) which showed that there was a

characteristic rhythm of white blood cells, with an interval of approximately an hour's duration, suggests that there is a very definite maturation interval. Weiskotten (1930) has worked out the normal life span of the neutrophilic leukocyte to be about four days in the rabbit, and it seems probable that it is about the same in the human. Roberts and Kracke (1931) believe that there are three definite onsets in Neutropenia. The first is in the marrow when there is disappearance of the cells of the myelocytic series. The second is four days later when the neutrophiles are absent from the circulation; and the third is one or two days after this when dramatic clinical symptoms present themselves. It is unnecessary to emphasize that these workers believe Neutropenia to be primarily a blood disease.

All physicians are convinced that the granulocytes are of very great importance in combating infection. These cells are probably the source of complement as they disintegrate, and they may also be important in the formation of the various immune bodies. Roberts and Kracke (1931) go so far as to state that neutrophiles are essential to life, and in reviewing their eight thousand cases in which they found leukopenic blood pictures in twenty-five percent, they

found also that complaints of weakness and fatigue were twice as frequent in the leukopenic group. The severity of the symptoms seemed to parallel the degree of reduction in the leukocytes. These authors made the further interesting observation that in those diseases in which there is a leukopenia there is always an associated collapse ( typhoid, dengue, influenza, etc.,) and in those diseases having a leucocytosis there is usually good strength and optimism (meningitis, pneumonia, pregnancy, etc.). Hence, it may be concluded that the lack of neutrophiles is an important factor in the causation of mental and physical collapse or exhaustion.

#### Pathology of the Bone-marrow

Studies of the bone-marrow in fatal cases of Neutropenia have shown that there are two rather definite conditions which may be present. In the first the marrow is aplastic due to a depression of granulopoiesis with cessation of maturation of the cells in this line. Also, there are evidences of marked degeneration and liquefaction of the tissue due to the absence of the support of the granulocytic tissue. Usually there is no interference with erythropoiesis so that the organ appears crowded with red cells in various stages

of development. This apparent erythropoietic hyperplasia may be entirely relative and be caused by the total lack of all neutrophilic cells. Lymphocytes and monocytes are always present in the marrow in this condition. Areas of patchy necrosis are visible throughout the tissue and there may also be infection of the marrow itself with bacteria present in rather large numbers although this condition, when found, is thought to be secondary to the breakdown of the barriers to infection. Beck (1933 a) has designated this picture as typical of Malignant Neutropenia.

In the second type, the picture presented in the bone-marrow is one of hyperplasia of the more immature granulocytic elements. Apparently maturation has not been interfered with until the cells are nearly mature, and the main difficulty is delivery of the cells into the circulation. Beck designates the condition in which this type of marrow is found as Benign Neutropenia. Fitz-Hugh and Krumbhaar (1932) consider it to be somewhat similar to Pernicious Anemia except that a different line of cells is affected, and therefore these workers are seeking for some substance comparable to liver for the treatment of Neutropenia.

In a remarkably complete analysis of the



microscopic findings of the marrow cells, Jaffé notes that in both the benign and malignant types, as here presented, there are regressive changes in the neutrophilic cells and that these changes are the essential pathology of the disease. First, the specific granulations are affected and dissolve, leaving vacuoles, and following this the oxydase reaction cannot be obtained. Next, nuclear changes appear and when this has happened the cell dies. These changes may be observed in all of the cells of the neutrophilic line beyond the myeloblasts. This investigator, Jaffé, is convinced that Neutropenia is not a disease entity but is merely a symptom complex as there is no difference between the condition of the blood and marrow in typical cases and in cases in which some very definite septic or toxic process has been known to have acted.

Roberts and Kracke (1930) have suggested that the two marrow conditions may illustrate different stages in the disease. They believe that the blood abnormality is primary and that it is capable of causing death if not arrested. They also believe that the secondary sepsis may cause death. And finally, they think that when the aplastic marrow is found it is a sign that recovery has begun in the hemopoietic

tissues but that death has been caused by an intoxication or sepsis which was too far advanced to be halted.

Jaffé quotes Zilowsky as suggesting the possibility that a blockade to cell delivery may be the primary factor, and that this may cause crowding of the marrow, first, and lead to a subsequent aplasia resulting from a kind of atrophy of disuse with degeneration. This explanation of the two types of bone-marrow pictures in Neutropenia is quite ingenious and further study may show that it has some merit although at present it is not taken very seriously.

The bone-marrow pathology is very definitely reflected in the peripheral blood and for that reason a discussion of the blood count will be undertaken at this time. The first abnormality usually noted is the marked decrease in the total white cell count to less than three thousand cells very early in the disease, and to only a few hundred cells after a few days. The beginning of the drop in the number of leucocytes in the circulation is believed to occur about three or four days after the onset of marrow pathology, or at the time at which those cells already present in the blood have become senile and begun to die out. The reduction in count is due to the diminished number

of neutrophiles at first, and only somewhat later is there also a decrease in the absolute number of lymphocytes. Eosinophiles and basophiles are usually present in normal numbers in the blood.

It is remarkable that no bizarre or abnormal cells of any kind are found in the blood of a typical case of Neutropenia, except occasionally as a terminal event. In rare cases there is a sudden appearance of large numbers of immature myelocytes just before death. It is probable that this occurrence indicates that the case is one of that type in which the bone-marrow shows myeloid hyperplasia and some unknown terminal event occurs which causes the release of a shower of stored immature cells. As yet there is no explanation of conditions leading up to this event.

The erythrocytes are entirely normal in character and in number until very late in the disease when general sepsis or toxemia may cause an anemia to develop. This never happens for at least ten days. The platelets are also normal unless the case is unusually prolonged.

Rutledge in 1930 reported a remarkable case of recurrent Neutropenia of which he has made very complete observations over a long period of time; he finds with supra-vital staining methods that the motility

of those neutrophiles seen in the blood stream before or during an attack is much diminished. This indicates that there may be some definite abnormality of the granulocytes themselves, but so far we have no clue as to just what type of abnormality it is.

### Pathogenesis

A number of general factors of importance in the pathogenesis of this disease have been discussed earlier in this paper. At the present time attention will be given to those factors which refer directly to the hemopoietic system. It is apparent that the reduction in the number of neutrophiles in the blood is due to destruction of large numbers of cells, to their abnormal distribution, or to the failure of normal cell development. The first possibility, destruction of large numbers of neutrophiles, is improbable because animal experimentation has shown no toxic agent to be present in the blood of patients suffering from the disease. In proving this, injections of blood from moribund patients were made into healthy animals and no bad effects were noted. In addition, patient's blood has been incubated with normal blood for forty-eight hours and cell counts made at frequent intervals. There was no evidence of abnormal cell destruction at

the end of the two day interval. Furthermore, the fact that the red cells remain normal in persons mortally ill with Neutropenia is strong evidence that the serum contains no toxic substance.

The second possibility to be considered, abnormal cell distribution, has been negated by check counts on venous and capillary blood and by examination of all of the organs after death for unusual cell accumulations. The third possibility, that of some developmental arrest, seems likely since the condition of the marrow in so many instances shows aplasia of the granular elements. The agent causing such a granulopoietic depression is thus far unknown.

Rose and Houser (1929) bring out the fact that earlier investigators considered some specific bacterial agent to be the etiological factor in Neutropenia. However, the fact that the disease has never been epidemic and that injections of the blood of patients into animals has not been harmful in any instance to the animals have made it necessary to conclude that infection, although frequently present, is probably secondary and non-specific. It has been possible to produce a state which closely simulates Neutropenia by means of bacteria, however, and several investigators have made use of this fact to facilitate

their study of the syndrome. Linthicum (1927) cultured *B. Pyocyaneus* from a fatal case of ulcerative stomatitis and called attention to the work of Geoghiewshi in 1899 which showed that this organism contains a leucocyte destroying ferment. Linthicum therefore experimented with the bacillus which he had isolated and managed to produce leukopenia in some guinea pigs. The lack of success in all animals is further evidence that the organism is not entirely specific. Fried and Dameshek (1932) produced granulocytopenia by injections of cultures of *Salmonella Suipestifer* and these workers were impressed by the remarkable similarity between the condition of Neutropenia in man and the syndrome in this type of sepsis in rabbits. The persistent neutropenia and necrosis in the marrow were very suggestive, as well as the fact that recovery, in those cases in which only small doses of the organisms had been used, revealed marrow and blood pictures similar to those in recovered cases of Neutropenia. It is obvious from this that some workers still feel that although no specific infective agent has been found in this disease, there is still the possibility that there may be one.

The most important work in this field is that which has been done by Dennis in the last two

years. This worker observed the fact that certain pyogens were capable of producing a leukocidin which was specific and lethal for granulocytes, and that these same pyogens were the ones most often associated with focal infections ( Staphylococcus Aureus, Streptococcus Hemolyticus and Viridans, and Bacillus Proteus).

Following the lines suggested by his observations, Dennis sealed eighteen hour cultures of these different organisms in parchment capsules and placed them aseptically in the abdominal cavities of experimental animals. Blood counts were than done on these animals several times a day and it was noted that a neutropenia developed which lasted for several months. After a rather protracted period of leukopenia, all of the animals died of intercurrent infection with some organism other than the one used experimentally. The similarity between clinical and experimental cases is further emphasized by the fact that the blood never showed any abnormalities in the red cells or in the platelets.

Control animals in which capsules of sterile broth were used showed no neutropenia and appeared to be perfectly well. It is of interest , as well, that measures which usually cause a leukocytosis, especially infection and X-ray, seemed to hasten the

exhaustion and death of the animal. This may have some application in regard to the extreme therapeutic activity usually seen in cases of Neutropenia.

Dennis considered that the specificity of the diffusible toxin indicated that it was a leukotoxin. Furthermore, he noted that injections of these same organisms or of their filtrates failed to produce similar findings. He therefore concluded that the restraint of the organisms from actually invading the tissue, as well as the constancy of the source of the toxin, were important factors. This author emphasized the fact that the conditions present in the ordinary focal infection may be of great importance in the etiology of Neutropenia. Unfortunately Dennis has not reported bone-marrow studies in the experimentally induced cases so that we do not know whether or not either of the typical marrow conditions are present.

The similarity of cases of known chemical poisoning to classical Neutropenia has forced investigators to consider certain poisons in relation to the etiology of this blood condition. Benzene seems most likely to be the offender in many instances as it is known to be a powerful leukotoxin which destroys the cells both in the circulating blood and in the hemopoietic organs. The myeloid tissue is more quickly



and more severely injured; in fact, it can be almost wholly destroyed by repeated injections of benzene. This type of poisoning, however, does not single out only the neutrophils but it goes further and causes a severe aplastic anemia (Hamilton 1931) which cannot be differentiated from the primary type except by history of exposure to benzene. Moreover, it is of importance that withdrawal of the chemical is quickly followed by regeneration of small islands of granulopoietic tissue in the marrow. These islands spread and cause the organ to appear practically normal within a few weeks. The small lymphocytes and polyblasts are most resistant and it is probable that they form the nucleus for regeneration (Selling 1916).

Kracke in 1932 attempted to see how closely he could simulate typical Neutropenia by means of small injections of benzene and he found that the smaller the dose given the more selective the drug in its affinity for granulocytes. A disease could be produced in which there was a marked neutropenia followed by a general septicemia, and he therefore feels that it is necessary to consider benzene as a possible etiological factor until we have found some truly specific cause for Neutropenia. It should be remembered, however, that benzene poisoning differs clinically from true

Neutropenia in that the mouth lesions seldom become necrotic, bacteremia is infrequent, and fever is absent or occurs only very late in the sickness.

Arsphenamine has also been observed to cause a condition closely simulating Neutropenia. However, it varies from the true disease in that recovery is prompt as soon as the drug is withdrawn. Foster (1930) considered that in his cases the intravenous use of sodium thiosulphate contributed to rapid recovery, but Farley's (1930) contention that the condition is merely benzene poisoning, as arsphenamine is benzene with arsenic substituted on the ring, would seem to deny that the thiosulphate could have any specific therapeutic value. Dodd (1928) studied the effect of arsphenamine on the hemopoietic organs and found that there was a primary stimulation, followed by a depression, especially of neutrophils. The similarity of his observations to the findings in benzene poisoning suggests that Farley is right and that some abnormality in the breakdown of arsphenamine frees benzene and causes poisoning by that agent. It is also probable that the Neutropenia noted after the use of the barbiturates and amidopyrine is of a similar type and due to abnormal reduction of the drugs.

Other workers attack the problem from a different angle entirely and are certain that there is a fundamental abnormality in the marrow itself. Doan in considering Sabin's work <sup>1925+</sup> (1932) on the rhythmic variations in the white blood count, concluded that the hourly fluctuations in the leucocytes must be caused by the death of many neutrophiles and by the almost immediate delivery of other cells into the blood. He was certain that the inpouring of young cells was in some way brought about by this wholesale cell destruction which preceded it, and he went further and considered the nucleotides to be or to contain the vital substance. This worker therefore attempted to produce unrestrained myelopoiesis by injections of sodium nucleinate and his work showed that there was an almost immediate and a sustained leukocytosis. On autopsy the animals all showed hyperplasia of the granulopoietic tissue with many ectopic foci in the kidneys and spleen. In consequence, Doan (1932) concluded that the nucleotides were the stimulating factor in cell delivery and that this caused a secondary myelopoiesis to meet the demand. Some therapeutic benefit may therefore be derived from nucleotides in those cases of Neutropenia in which the marrow is hyperplastic.

The possibility of there being some endocrine

mechanism involved in maturation or delivery of cells has been suggested frequently and therefore must not be entirely omitted from this discussion. However, in the study of Neutropenia there have been no findings so far which direct attention toward any particular hormone or gland with sufficient definiteness to suggest the lines for further investigation to follow.

#### DIFFERENTIAL DIAGNOSIS

The diagnosis of Neutropenia is based mainly on the blood count which shows a leukopenia with a marked reduction in the number of granulocytes. Later in the disease there is also some reduction in the absolute number of lymphocytes. No abnormal cell forms are to be seen in the blood at any time with the exception of the terminal stage when there may be a shower of immature neutrophils. The red count and platelet count remain normal throughout the illness unless it is unusually prolonged. In addition, the symptoms of exhaustion and fever are found in all cases and there may also be considerable secondary infection, necrosis, and ulceration on the mucous surfaces.

As a number of conditions may be confused with typical Neutropenia it is my aim at this time

to indicate briefly some of the differential points in the diagnosis.

(1) Acute leukopenic leukemias can usually be differentiated from Neutropenia by the blood pictures, as abnormal cells are almost always to be found in any leukemic conditions even when the total count is low. Furthermore, the platelets are diminished and hemorrhages from mucous surfaces are usual, and the combination of these hemorrhages with fundamental marrow disease soon leads to the development of a severe secondary anemia. Beck (1933 a) states that an absolute differentiation may be impossible in some cases, however, although a biopsy of the marrow may be of great help. The prognosis is uniformly poor in both conditions so that differential diagnosis of these two diseases is of more academic than clinical interest.

(2) Several cases of acute monocytic leukemia have been reported in the last few years and since this condition is rare, unlike other acute leukemias, and not found in the older textbooks it is apt to be entirely missed. In this condition there are two types of cells which suggest the blood diagnosis, first, the usual monocytes and, second, cells which appear to be like clasmatocytes. The typically low

neutrophilic count, inflammation of the gums, fever, and weakness are all confusing but in Monocytic Leukemia there are never any typical necrotizing areas and the total leucocyte count is almost always higher than normal. The clinical condition is so confusing that diagnosis may be possible from the blood examination only. The leukocytes are usually between fifteen and forty-five thousand with a preponderance of large monocytic cells up to seventy percent and the clear identification of these cells is of great importance. There is never complete disappearance of the polymorphs and in some cases where there is no rise in the total count it may be necessary to determine the absolute number of monocytes as well as the presence of histiocytes in the blood. The fact that in the course of the illness this is apt to become a mixed leukemoid type makes many investigators consider that it is simply the reflection of some irritation of the reticular system. On the other hand, the fact that some cases are so definite and that death is usually in about ten weeks suggests that it is a clinical entity.

(3) Infectious Mononucleosis is another condition which may be confused with Neutropenia and is therefore worth careful consideration at this time.

The disease is clinically characterized by enlargement of the lymph glands, low grade fever, and weakness; there may also be an associated membranous angina. Typically the blood findings give the diagnosis as there is a marked leukocytosis and the blood film shows all varieties of abnormal lymphocytes. The red cells are normal also.

There are cases, however, in which the blood count remains low, with a large proportion of lymphocytes, and unless careful differential counts are done the diagnosis may be missed as it is based only on the presence of bizarre cell types. Recently Bunnell (1933) has reported a remarkably specific laboratory test for this disease by means of sheep cell agglutination. This will be very helpful if it proves accurate in borderline cases. Because of the great difference in the prognosis in these two conditions, Neutropenia and Infectious Mononucleosis, an accurate diagnosis is of great importance. In Infectious Mononucleosis the illness may be protracted and there may be remissions but ultimately good health is regained.

(4) Aleukia is characterized by extreme generalized aplasia of the bone-marrow. Although this condition and Neutropenia have similar blood findings in the first twenty-four hours, the rapidly

developing anemia, the tendency to hemorrhage, and the thrombocytopenia should point to the true diagnosis within a few days.

(5) Aplastic anemia with sepsis has also caused confusion in the early stages. The onset, however, is never abrupt, as in Neutropenia, there are subsequent hemorrhages, and the advancing hyperchromic type of anemia is diagnostic.

(6) Septicemia;— In spite of the fact that Jaffé insists that Neutropenia is merely a symptom complex and may be due to sepsis, a distinction will be made between the two conditions. The hemorrhages, secondary anemia, abscesses, and presence of immature granulocytes in the circulating blood all serve to label the condition as quite different from typical Neutropenia .

(7) Lymphosarcoma must be ruled out by the clinical course and by biopsy of the marrow.

(8) Hodgkin's disease will seldom if ever be confused with Neutropenia. In any case in which there is any doubt a biopsy of the glands is sufficient to settle the question. This is usually unnecessary as the blood count almost never shows a diminishing number of neutrophils.

(9) Dengue occurs with a marked leukopenia



in which the granular cells are reduced but the disease can be differentiated clinically by the characteristic rheumatic pains.

(10) In Scarlet Fever there may be a relative decrease in the neutrophiles rather late in the disease but at this time there is seldom doubt as to the diagnosis.

(11) Diseases having mouth or throat ulcers such as Diphtheria, Vincent's Angina, Monocytic Angina, and Tonsillitis may be confusing clinically but the blood picture will settle any doubts.

(12) Benzene poisoning has been discussed as a possible cause of Neutropenia, but it is generally accepted that it differs in several respects. In this condition there are rarely any ulcers or gangrene, the fever is not high until very late, and the history of exposure to benzene, arsphenamine, or barbitals can usually be obtained. The chief differentiation depends on the fact that benzene tends to destroy all myeloid tissue so that an aplastic anemia as well as a leukopenia is soon found.

#### SUMMARY

1. Neutropenia as a clinical condition has been reviewed. Its occurrence, symptomatology, classi-

fication, pathology, treatment, and prognosis have been covered briefly.

2. A short discussion of the theories of hematopoiesis , with special emphasis on the anatomy and physiology of the granulopoietic tissues, has been given, since the interpretation of the blood picture in Neutropenia depends on a good understanding of the underlying mechanisms.

3. The pathology of the myeloid tissues has been discussed at some length and has been considered in relation to the theories of pathogenesis of Neutropenia.

4. Consideration has been given to the differential diagnosis between Neutropenia and twelve other conditions.

CASE HISTORIES

1. From Zininger- 1934 (see page 7)

A woman 63 years old. The past history was not important. The present illness began in April 1932 when she complained of extreme fatigability, and was put to bed with the diagnosis of influenza. A blood count April 26 showed 250 leukocytes with no neutrophils. A number of small necrotic areas were noted on the skin of her fingers at this time. She was given one roentgen treatment and then injections of leukocyte extract for six days; later she was also given a few doses of pentnucleotide.

The return of immature granulocytes to the blood began the fifth day after the treatment with leukocyte extract was started and the count rose to 31,000. The granular cells appeared first as myeloblasts and progressed to maturity.

An area of superficial gangrene was also present in the right axillary region and there was accompanying thrombosis of the veins of the right arm. After the granulocytes returned to the circulation pus appeared in all the necrotic areas and the lesions went on to heal in about six weeks. Recovery seemed to be complete in the summer and several blood counts taken during the next year were normal.

One year later, April 13, 1933, the patient noted that abrasions on her fingers were not healing properly and she felt tired and had no appetite. At this time her blood count showed 2,500 white cells with no neutrophils. Pentnucleotide and intramuscular liver extract were given without result. Finally leukocytic extract was given for three days. There were no special subjective symptoms until the 21<sup>st</sup> of April, though there were several indurated areas which developed in the skin. On April 21 the patient collapsed; her fever was 103°; she developed auricular fibrillation, and some rales at both bases. Digitalis was effective in treating the heart condition but pneumonia developed and lasted for some time.

On May 1 the patient was given 10 units of adisin. There was no change in the blood picture until May 8 when many polys, both mature and immature, appeared in the blood and the blood count rose within a short time to 36,300. The general condition did not change except that the skin indurations abscessed. The patient died June 15.

At autopsy there were the expected findings of a fibrinous plury, abscesses in the lungs, spleen, kidney, etc., and general degenerative changes in the organs. The bone-marrow showed active regeneration.

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2. From Zininger 1934 (see page 7)

A woman, aged 56, having an arthritic deformity of the right hip, became ill in March 1933 with a number of furuncles on her neck, hands, and arms. She treated herself for sometime but on March 21 she suddenly became very weak and sick and it was noted that the skin lesions were not abscesses but red, indurated nodules having necrotic centers. A blood count showed only 477 leukocytes with no granulocytes. Pentnucleotide was started at once and seven doses were given but the patient did not respond and died on March 24th.

It is interesting to note that cases 1 and 2 were sisters, who lived together, and died at about the same time of a similar disease. There have been no other instances carrying the same implications of contagion or hereditary etiology. Also the skin lesions are not the usual manifestations.

3. From Rutledge, Hansen-Pruss, Thayer 1930

(see page 9)

A case of recurrent granulocytopenia has been reported. This began when the infant, male, was eight weeks old and had anuria which responded to treatment with hot packs. This recurred several times; and the infant was always difficult to feed, subject to

digestive upsets with diarrhea, and to furunculosis. It was noted that these attacks were always accompanied by a leukopenia but that the red cell count remained normal. After treatment with autogenous vaccine the furuncles ceased but the attacks of diarrhea and stomatitis continued to recur about every three weeks throughout his boyhood. The temperature would rise to 100-103° and the lymph glands would swell usually. The character of the attacks changed somewhat as he became older and consisted of fever, some stupor, anorexia, and vomiting, but no bowel abnormality. The leukopenia with granulocytic depression was always present, and the white cells frequently went to about 800 cells per cubic millimeter. No abnormalities were found on physical examination between attacks.

In 1928 the patient was hospitalized and studied carefully through several attacks (19 years of age at this time). He was found to be normal physically except that he was somewhat undeveloped. His disposition was difficult. The blood count was normal in every way, when taken between attacks. All laboratory work was negative.

His attacks occurred at about three week intervals and were ushered in by listlessness, fatigue, stomatitis, and enlargement of the cervical lymph glands.

His temperature rose for about four days and fell in six or eight days as the symptoms subsided. The blood count fell to about 2,000 cells with many abnormal cells and a high percentage of eosinophiles and monocytes at the peak of the attack, and with recovery the leukocytes became normal in number and morphology.

This case is unique in its course and therefore is of great importance in the study of Neutropenia. The appearance of abnormal cell types during the attacks is not explained by the authors.

4. From Kracke 1931 (see page 9)

A woman, aged 44, gave a history of having had bilateral salpingitis in 1915, otitis media after Scarlet Fever in 1918, and many colds for which she had taken vaccine therapy several times. For a period of five years she had had recurring attacks of weakness which necessitated rest in bed for several days at a time.

In May 1930 she had a temperature of 102', and was very weak but complained of no pain. There were no physical findings of importance, and the leukocyte count was 900 with no neutrophiles. On May 21, she was given X-ray therapy and the leukocytes rose to 2,600. She was given two more X-ray treatments, and also a transfusion and recovered sufficiently to

leave the hospital by June 4, though her white count was only 2400 with 79% neutrophiles.

On June 28 she developed a hydrothorax and the leukocytes fell from 4500 to 2500 in two days. She remained in the hospital until July 16.

Two and one-half months later she had another attack of sudden weakness, following a tooth extraction, and her leukocytes dropped to 900 with no granulocytes. The neutrophiles never reappeared in her blood and she died October 22. No autopsy was done.

5. From Fisher 1930 (see page 17)

A nurse 24 years old reported to the dentist because of sore gums and was given neo-salvarsan for a Vincent's angina. In the afternoon of the same day she had a chill, developed a sore throat, and vomited. The following day she had a fever of 102', and felt acutely ill. The throat was swollen and red and there was a dirty gray exudate on the gums. The cervical and sub-maxillary lymph glands were large and tender and there was cellulitis on the right side of the neck.

The physical and laboratory findings were otherwise negative except for a leukopenia with only 6% neutrophiles. She was given a transfusion of 500 cc. of blood which did not seem to benefit her. Two days later



she was given 25 million dead typhoid germs and one ampoule of sodium nucleate with no apparent benefit. After this she was given a transfusion from a donor who had been sick in 1927 with Neutropenia and had recovered entirely. The patient became subjectively better at once, her temperature started to drop, and her leukocyte count rose to 1,200 . She was given more sodium nucleate and later had two hemorrhages and was given a transfusion from an ordinary donor to replace this blood. She made an uneventful recovery.

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6. From Beck 1933 a

A white woman, 58, became ill on March 22, 1929 with a sore throat, backache, a chill, and nausea. She grew progressively weaker and the following day a study of the blood showed that she had a white cell count of 700 with normal red cells and hemoglobin. Her throat was inflamed and one tonsil ulcerated. She was given 1/20 of an erythema dose of X-ray at this time, and it was repeated on March 25.

The blood culture was positive, and she became worse; the mouth lesions, vomiting, anorexia, and weakness all progressed. Ten cc. of leukocytic extract and ten cc. of whole blood were given subcutaneously and the same day she also received a trans-

fusion of 750 cc. of whole blood. She became worse and was given sterile milk subcutaneously. On March 28, she was given another transfusion but became worse, sank into coma and died. Just before death there was an agonal rise in the leukocytes to 2,300.

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7. From Doan 1932

A woman, 36 years old, on November 20th had a tooth extracted and three days later complained of general malaise and extreme soreness at the site of the extraction. On the 24th she was prostrated and suffered from vomiting and epistaxis; her temperature was 101° at this time and the pulse 120. Blood study showed the leukocytes to be only 1500 with 22 % neutrophils, and the blood culture was positive for B. Subtilis. By the 28th of November the blood count was 1400 with 2% neutrophils and she was given pentose nucleotide for the next five days. A gradual rise in the numbers of granulocytes began on the 29th and continued for a month when the count was 11,000 with 56% neutrophils. The red count and hemoglobin remained normal at all times. This patient made an uneventful recovery.

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