GRANULOPENIA (AGRANULOCYTOSIS)

RUSSELL L. HADEN, M.D.

In 1922, Schultz[1] described four patients with gangrenous throat lesions and marked leukopenia due to a decrease or absence of granular cells from the peripheral blood. The patients were all women of middle age, all died, and at autopsy very few myeloid cells were found in the bone marrow. Schultz designated the condition, agranulocytosis, and considered it a definite clinical entity. Since this first report, many similar cases have been reported, largely from Germany and America. Numerous names other than agranulocytosis, such as, agranulocytic angina, malignant neutropenia, idiopathic neutropenia, pernicious leukopenia, granulocytopenia, and granulopenia have been suggested to indicate the syndrome described by Schultz. The word, granulopenia, best describes the condition since it is primarily a decrease in the granular cells of the blood. Idiopathic granulopenia refers to granulopenia occurring without apparent cause. The subject has been in a confused state but increasing study suggests that leukopenia and necrotic lesions represent a symptom complex and not a clinical entity. It is now known that every degree of severity of both clinical symptoms and blood findings may be encountered. What Schultz observed was a high degree of bone marrow involvement which often occurs in much milder form as a result of the same etiologic agent or agents. It is now also evident that changes observed in the peripheral blood only reflect bone marrow disease, so no correct picture of the condition is possible without correlating the pathology of the bone marrow with the clinical and laboratory findings. This has been well emphasized by Dean.[2] I have considered in this paper the group of conditions in which a granulopenia of the peripheral blood is observed with or without local necrotizing lesions in relation to the hematopoietic system as a whole.

The Clinical Picture—The syndrome which Schultz[1] described was characterized by an acute onset, prostration, fever, chills, gangrenous mucosal lesions, and marked leukopenia. Further study has added little to this clinical description except the recognition of milder forms. The leukopenia is due to a great decrease or complete absence of granulocytes. The ulceration may involve the cervix, vagina, penis, rectum or anal area as well as the throat, so there are no constant local lesions. The characteristic blood findings may be observed in the entire absence of necrosis, and the disease is not necessarily fatal. Recovery is not uncommon in both the mild and the severe cases. Numerous cases of recurrence have been described in which there has been a great variation in signs and symptoms with different attacks. Weakness, however, seems to be a striking and almost constant symptom of

granulopenia. Exactly the same clinical picture may be observed in cases in which leukemia is later proved to be present.

All the evidence indicates that the ulcerative lesions are secondary to the decrease in granulocytes and consequent loss of their normal defensive power. Numerous bacteriologic studies have demonstrated organisms of many kinds in the local lesions without any one predominating. Blood cultures made during the height of clinical symptoms frequently give positive findings, but a variety of organisms has been recovered. Local or general infections once established may be an important factor in the final outcome, but it seems evident that bacteria have little to do with the primary injury. In cryptic or idiopathic granulopenia, an overwhelming infection of any type may, however, cause the same picture, but here the primary disease is self-evident.

Etiology—Many different causes of granulopenia have been considered, but bacteria and chemicals have been most prominent. It has long been known that certain drugs, as benzol and arsphenamine will produce a profound leukopenia by a depressing action on the marrow. Usually, however, all elements of the marrow are affected by such agents. Kracke[3] attempted to reproduce the disease in rabbits by the use of various oxidation products of benzene, aniline dyes, and drugs of the coal tar derivatives. He found that benzene given subcutaneously in small amounts showed a selective affinity for the myelocytic tissues with resultant peripheral leukopenia and frequent infection. He suggested that substances which contain the benzene ring should be strongly considered as the cause of granulopenia. Since not infrequently a marked leukopenia has been observed in overwhelming infections, either local or general, numerous attempts have been made to reproduce the condition with organisms recovered from local lesions, or from the blood of patients suffering from the disease, with but little success. While it is true that marked myeloid depression may be produced by certain bacteria, no one organism gives constant results experimentally or is regularly recovered from the affected individuals.

Radiant energy will produce a marked leukopenia, but this can be eliminated as a possible cause in most cases of granulopenia. A blood picture and often clinical findings identical with those of cryptic granulopenia may be observed in splenomegaly, especially Banti's disease, leukopenic leukemia, pernicious anemia, and aplastic anemia. Usually in such cases all elements of the bone marrow are affected, but at times the involvement of myeloblastic tissues is predominant, so that the leukopenia is all out of proportion to the erythropenia and thrombopenia.

The most important contribution to the etiology of cryptic granulopenia has been the proof that certain commonly used drugs, princi-

pally amidopyrine, and especially in drug sensitive individuals, may specifically depress the myeloid tissue of the marrow. Kracke[3] noted that eight of nine patients with granulopenia of undetermined origin had been taking drugs of the coal tar series prior to the onset of clinical symptoms. He was unable to affect the leukocyte count experimentally, however, with such drugs. Madison and Squier[4] were the first to incriminate definitely amidopyrine, especially in combination with a barbiturate as the cause of granulopenia. They found that the onset of granulopenia was often directly preceded by the use of amidopyrine alone or in combination. Several of their patients were known to have a normal blood count or even a leukocytosis before the use of the drug. They also found that a profound granulopenia again developed in two patients, who after recovering from an attack, took a single dose of amidopyrine. Additional evidence that amidopyrine and similar drugs are the most important etiologic agents in cryptic granulopenia is rapidly accumulating.

The Activity and Lability of Normal Bone Marrow—Although all tissues of the body are constantly being torn down and built up, the bone marrow is one of the most active of all. The bone marrow should be looked on as an organ,[5] and one of the largest in the body (about 1500 cc.). The striking activity of the marrow is well shown in its relation to erythrocyte formation. A red cell lives in the circulation from two to four weeks. If we take twenty-five days as the mean span, 1/25 of the entire mass of red cells, or about one trillion erythrocytes, must reach maturity and be discharged from the marrow every day. The life span of the granulocyte in the human is unknown, but it is probably very short—possibly only a few hours and certainly not more than a few days. There are roughly twenty-five billion granulocytes in the circulating blood of a normal adult, so at least from five to twenty-five billion granulocytes must mature and be released from the marrow every twenty-four hours. There is a rapid, continuous process of growth and maturation. Every granulocytosis and every granulopenia represents a disturbance in this normal rhythm. The process of development in the marrow may be conveniently grouped into three stages. The first is the stage of origin. Here the primitive white cell develops from the reticulum cell, and in time becomes a myeloblast, and then an early myelocyte. Multiplication may take place in all four cells but is most active in the early myelocyte stage. Proliferation now ceases, and differentiation of each cell into the mature neutrophil through successive stages of nuclear growth and development follows. The third stage is that of emergence or delivery into the circulation. The circulating stage is short and of little physiologic importance since the white cell functions locally at some point reached by the blood stream rather than in the circulating blood as does the red cell. A

disturbance of the granulocyte may involve any or all of these different stages. It is especially important to remember that to function normally at the site of final localization, the granulocyte must be qualitatively normal as well as quantitatively sufficient. Too little emphasis has been laid on the qualitative changes. After emergence, the granulocytes undergo no further differentiation or change in the circulating blood. Thus, the condition of the cells in the circulation is due to the state of the marrow. Changes in the marrow always precede those in the circulating blood.

The Bone Marrow in Granulopenia—Schultz[1] found a striking absence of myeloid cells in the bone marrow of the patients he described. There was little involvement of the erythroblastic tissue which accounted for the absence of anemia. Other observers likewise report an aplasia of the granulocytic elements of the bone marrow, but further studies have shown, however, that the peripheral leukopenia does not necessarily mean a bone marrow aplasia. Fitz-Hugh and Comroe[6] in nine autopsies found myeloid hyperplasia in more than half. This finding they think confirms the idea of "maturation arrest" previously suggested by Fitz-Hugh and Krumbhaar[7] as the fundamental disturbance rather than myeloid aplasia. Jaffé[8] concludes from autopsy studies in nine cases that the myelocytes bear the brunt of some toxic action on the marrow with evidence of degenerative changes. He found this identical characteristic picture in neutropenia due to salvarsan (2 cases), overwhelming infection with granulopenia (2 cases), and in the so-called idiopathic granulopenia (5 cases). The marrow was active but toxic, so that normal multiplication and maturation either in quantity or quality could not go on. Fried and Dameshek[9] found a great variation in the bone marrow even in constant peripheral leukopenia in experimental granulopenia in rabbits injected with Salmonella suipestifer. Schilowa[10] likewise found a great variation in the bone marrow picture in benzol poisoning in dogs. Some animals showed hyperplasia, others aplasia. While benzol poisoning typically causes a leukopenia and thrombopenia, in some animals there was a leukocytosis and thrombocytosis. These findings are easy to understand when we realize that many agents which destroy in larger doses will stimulate in smaller amounts. Radiant energy is a classic example of this fact. A case of benzol poisoning in a man who had anemia and neutropenia has been reported recently by Anderson[11] in which the autopsy showed hyperplasia of the marrow. Jackson and Parker[12] have studied at autopsy the bone marrow from twenty-five patients who had this disease. In patients dying early in the course of the disease, they found little gross change in the marrow, and no involvement of the red cell series or megakaryocytes. There was a striking absence of cells of the granular series, except stem cells which were plentiful and in

active mitosis. They conclude with Fitz-Hugh and Comroe[6] that "maturation arrest" is an important part of the picture. In patients who survived from eight to twenty days, the marrow was hypoplastic and even stem cells were scarce.

In summary, one may say that there is no characteristic marrow picture in granulopenia except usually, predominant involvement of myeloid cells which are affected both quantitatively and qualitatively. The marrow findings depend upon the stage of the disease and the extent of damage as well as upon the effect of secondary factors, such as infection. In any event, it is evident that the peripheral blood findings result from the marrow disease. It is also evident that the marrow changes are no different in leukopenia due to marrow toxemia caused by known agents than in that due to unknown agents (so-called idiopathic granulopenia).

The Blood Findings in Granulopenia—The one constant blood finding is leukopenia and granulopenia. The total white blood cell count may vary from a few hundred cells to 2500. The lowest number I have seen is 100 cells. The count is seldom higher than 2500 cells during the active stages of the disease. Marked local infections may occur, and there may be a moderately low count while infection may be minimal with an extremely low count. The granulopenia is the predominant change, but in the very low counts there is necessarily a decrease in lymphocytes and monocytes as well as in granulocytes. Patients with extreme anemia and thrombopenia are usually excluded, although almost always some degree of anemia is present. Schultz[1] emphasized the absence of anemia, and this has usually been considered an essential part of the clinical picture. However, with marked myeloid involvement there is almost always some change in the red cells and platelets.

Qualitative changes in such granulocytes as are found in the peripheral blood are striking and have been given too little attention. The circulating granulocytes are seldom normal qualitatively. The nuclei often show pyknosis and other variations from normal in the chromatin-parachromatic pattern. The most striking changes, however, are in the granules and cytoplasm. The granules are decreased in number, vary greatly in size, and show increased basophilic staining. The cytoplasm often shows vacuoles. The cells may be swollen and much larger than normal. As Jaffé[8] has emphasized, such changes are all evidence of some toxic effect on the granulocytes in the marrow.

Classification of Granulopenia—Since I have emphasized that so-called idiopathic granulopenia is only a reflection of bone marrow disease, it is important to have clearly in mind the relation of the different types of leukopenia and granulopenia to changes in the mar-

row. The following classification attempts to correlate the varying clinical and pathologic pictures in cases characterized by peripheral leukopenia:

Classification of Granulopenia

I. ***Granulopenia*** with decrease in erythrocytes and thrombocytes from aplasia or hypoplasia of all bone marrow cells due to:

1. Infection
2. Radiant energy
3. Chemicals as arsphenamine or benzol
4. Diseases of the spleen as Banti's disease
5. Unknown causes (idiopathic)

II. ***Granulopenia*** due to mechanical interference with delivery of mature granulocytes in:

1. Hyperplasia of myeloblastic tissue with leukemia or myeloma
2. Hyperplasia of erythroblastic tissue in pernicious anemia

III. ***Granulopenia*** due to selective interference with multiplication, maturation or delivery of granulocytes from the marrow by:

1. Chemicals as amidopyrine and phenobarbital
2. Allergic reactions
3. Infection
4. Radiant energy
5. Unknown causes (idiopathic)

Illustrative Cases

I. Granulopenia with Decrease in Erythrocytes, Thrombocytes and Myeloid Cells from Aplasia or Hypoplasia of All Elements of Bone Marrow due to:

(a) Sulpharsphenamine—A.E.C., a merchant, thirty-nine years old, received twelve injections of sulpharsphenamine from April to November, 1932. In December, 1932, he was confined to bed because of chills, fever, weakness, and pain in the back. At this time he was very pale and dyspneic. The first blood examination made January 27, 1933, showed 1,100,000 red blood cells, 4,300 white cells, and a hemoglobin content of 20 per cent. No local infections were present. Several blood transfusions were given, and improvement in the patient's condition resulted.

When the patient was first seen in the Cleveland Clinic, March 25, 1933, the examination revealed no findings of significance except for pallor and many petechiae. At this time, the red cells numbered 2,860,000, the hemoglobin content was 44 per cent, and the white cells numbered 2,000. The fragility of the erythrocytes was normal, the reticulocytes were less than 0.2 per cent, and the icteric index was 5. The thrombocytes numbered 10,000, the bleeding time was over 40 minutes, and clot retraction was absent. A differential count of the leukocytes showed 17 per cent neutrophils, 78 per cent lymphocytes, and 5 per cent monocytes. No abnormal white cells were seen. While the patient was under observation, the white cell count fell to 1,250, and there was almost entire absence of granulocytes. After further transfusion, pentnucleotide, and liver

therapy the patient continued to improve and when last heard from, he had returned to work.

In this case there was evident involvement of all elements of the marrow, although as judged by the peripheral blood findings the myeloid tissue was involved out of proportion to the erythroblastic tissue.

(b) Banti's Disease—B.C.G., a boy fourteen years old, during the course of a routine examination six years previously, was found to have a large spleen. He had been entirely well except for poor endurance on exercise. He had been advised to have the spleen removed and came to the Cleveland Clinic for confirmation of this advice.

On examination, there were no significant findings except a spleen which extended down to the crest of the ileum and to the right of the midline above the umbilicus. The Wassermann test gave negative findings and examination of the urine showed nothing of significance. Examination of the blood revealed 4,250,000 red cells, 68 per cent hemoglobin, and 1000 white cells with the following differential count—neutrophils, 53 per cent, eosinophils, 4 per cent, lymphocytes, 36 per cent, and monocytes, 7 per cent. The platelets numbered 140,000, and the icteric index was 5.

The leukopenia was evidently due to the splenic disease and produced no symptoms.

(c) Idiopathic Aplastic Anemia—F.C., a boy fifteen years old, had noticed soreness and bleeding of the tonsils one month before admission, and this was followed by petechiae and weakness. One week later, the neck became swollen, and the gums began to bleed. For two weeks blood had been present in the stools, and for one week in the urine.

Physical examination revealed the patient to be very pale; there were many petechiae over the body, and the gums were bleeding. There was no marked enlargement or ulceration of the tonsils. The spleen was not palpable, and the glands were not enlarged. The temperature was 103°F. Soon after admission, a large mass developed in the jaw which seemed to arise around an abscessed tooth. The spleen became larger, and the high temperature continued. Proctoscopic examination showed a large ulceration in the rectum. One week after admission, consolidation developed in the left lower lobe of the lung, and he died three days later.

The blood count on admission revealed 800,000 red blood cells, the hemoglobin content was 13 per cent, volume index 1.06, and color index 0.81. There were no signs of regeneration of the red cells. The white cell count was 400, with 46 per cent neutrophils, 50 per cent lymphocytes, and 4 per cent monocytes. No abnormal white cells were seen. The platelets numbered 20,000, the bleeding time was 45 minutes, and the coagulation time was 12 minutes (Lee and White method) without clot retraction. Three days before death, the white cell count was only 250.

The autopsy showed the spleen to be normal in size, and there was no evidence of leukemia. The bone marrow in the lumbar spine, sternum and ribs was grossly pale and fatty in the head of the tibia. Sections showed marked aplasia of the marrow with a large amount of fat and sparsely scattered indifferent mononuclear cells. No myelocytes and very few cells resembling granulocytes could be found.

II. Granulopenia Due to Mechanical Interference with Delivery of Mature Granulocytes in:

(a) Leukopenic Leukemia with Angina—M.L.L., housewife fifty-three years old, was first seen February 23, 1934, in the Nose and Throat Department of the Cleveland Clinic. She complained of sore throat which had been present for four weeks. Examination at that time revealed a necrotic, ulcerated area in the right tonsil, with deep excavation and slight cervical glandular enlargement. She had had an active arthritis several months before, and on admission she complained of pain in the left shoulder, but there was no objective evidence of arthritis. The examination was negative except for throat findings.

The initial blood examination showed 3,760,000 red blood cells, a hemoglobin content of 68 per cent, and 1,400 white blood cells with 19 per cent neutrophils, 80 per cent lymphocytes, and 1 per cent eosinophils. No abnormal white cells were seen. The patient was known to have an idiosyncrasy to quinine, but she gave no history of taking drugs which might cause a bone marrow depression. Under observation, this patient's throat lesion healed completely, although she continued to have fever. Several subcutaneous nodes developed, all of which resolved without evidence of active inflammation. Pentnucleotide, injections of liver extract intramuscularly, iron, and blood transfusions were administered. The leukopenia continued, but no immature cells were ever seen. The anemia was progressive, and the last blood count six months after admission showed only 700,000 red cells, 15 per cent hemoglobin, and 1,500 white cell. The white blood cell count was frequently below 1,000, and there was almost entire absence of granulocytes. In many examinations, no immature white cells were ever seen.

This patient died four months after leaving our care. At that time, the leukocyte count was 34,000, and many myeloctytes were present. Autopsy was refused.

This patient evidently had leukopenic leukemia from the onset of her illness, although the diagnosis was impossible from a study of the peripheral blood. No biopsy of the bone marrow was made. The early onset of a necrotic pharyngeal lesion with complete recovery from the local lesion is most unusual.

(b) Pernicious anemia—A.S., a widow sixty-two years old, was referred to the Cleveland Clinic with a diagnosis of carcinoma of the stomach. The physical examination revealed only an evident anemia. The neurological examination gave only negative findings. A roentgenographic study of the gastro-intestinal tract showed no evidence of disease. The test meal revealed achlorhydria. The blood examination showed 2,260,000 red cells, 55 per cent hemoglobin, volume index, 1.35 and color index, 1.22. The white cell count was only 2,000 with 34 per cent neutrophils, 57 per cent lymphocytes, 8 per cent eosinophils, and 1 per cent monocytes. With specific liver therapy, this patient's white blood cell count and other blood findings have returned to normal and have remained normal. The leukopenia here was due to enmeshment of the granulocytes in the hyperplastic red marrow.

III. Granulopenia Due to Selective Toxic Action on Myeloid Tissue in the Marrow By:

(a) Phenobarbital—M.F., a housewife twenty-eight years of age, was first seen in the Cleveland Clinic October 28, 1929. Functional vertigo was diagnosed, and phenobarbital was prescribed. A blood examination made at that

time showed 4,580,000 red cells, 80 per cent hemoglobin, and 6,700 leukocytes. One week later, a maculopapular eruption developed which was diagnosed measles. After a period of two weeks, another marked rash appeared which was first thought to be due to scarlet fever, but was later considered a drug rash. Two months later, the patient was admitted to the hospital, complaining of pain in the ear. At this time, her temperature was 103° F., and exfoliative dermatitis was present, but there was no throat lesion. Later, open sores appeared on the buttocks and on the back. The leukocyte count on admission was 2,400 with 1 per cent neutrophils, 1 per cent eosinophils, 1 per cent basophils, 2 per cent monocytes, and 94 per cent lymphocytes. The red blood cells numbered 3,700,000, and the hemoglobin content was 75 per cent. The white cell count fell as low as 1,000, and a marked anemia developed later. With transfusions and supportive therapy, the leukopenia disappeared, and the red cell count and hemoglobin returned to normal. The temperature was elevated for one month. The skin lesion cleared entirely. An alopecia developed.

Three years later, this patient was again admitted to the hospital for acute abdominal pain, and was given one and one-half grains of phenobarbital. Dermatitis with redness, swelling, and itching quickly developed. At this time the leukocyte count was 22,600 with 96 per cent neutrophils. Later, a reaction to morphine developed after operation, but no blood count was made.

This patient was known to be sensitive also to certain foods and to quinine. Granulopenia and dermatitis developed after the use of phenobarbital. The granulopenia was evidently due to myelotoxicosis, and later the red cells were involved also. At another time, a single dose of phenobarbital produced leukocytosis and a rash.

(b) Amidopyrine with Recurrent Angina and Granulopenia—R.E.H., a physician twenty-nine years of age, was perfectly well until September, 1932, when he had an illness of two weeks' duration which was diagnosed rheumatic fever. The joints were painful for one week, the spleen was palpable, and the attack was followed by generalized weakness for two months. The blood count at that time showed 5,000 leukocytes. In February, 1933, he began to have weakness accompanied by fever and chills. A blood count again showed 5,000 leukocytes. Similar minor attacks occurred twice in March and in early June, 1933. June 11, 1933, following the extraction of a tooth, a high temperature, chills and weakness developed, and this was followed by ulceration of the tongue and throat. The white cell count fell to 1,250, with complete absence of neutrophils. Five injections of pentnucleotide were given, and the blood count returned to normal, and the symptoms disappeared. In October, fever, chills, and weakness again developed. The white cell count fell to 700 with an absence of neutrophils, and the ulceration of the tongue and throat recurred. The patient was given four injections of pentnucleotide without response. On November 10, he had an attack of migraine. Nine days later, the white cell count was 3,100. Following this, fever and nasopharyngeal ulcerations were noticed. At this time, liver extract was given intramuscularly, and the white cell count rose to 6,000, and all symptoms subsided. When he was seen in the Cleveland Clinic, December 15, 1933—fifteen months after the onset of the illness—the red cells numbered 4,635,000, the hemoglobin was 95 per cent, and the white cells numbered 4,700 with 44 per cent neutrophils, 42 per cent lymphocytes, 4 per cent eosinophils, and 10 per cent monocytes.

The patient was not conscious of any drug sensitivity, but he had had migraine for many years for which he had taken allonal, phenobarbital and amidopyrine. Quinine had been used for the joint disturbance. He had been

taking one and one-half grains of phenobarbital twice a month previous to the onset of the illness. In September, he noted that on two occasions, two weeks apart, taking one allonal tablet induced a chill the following day.

The patient had kept a careful blood count record for a long time. After the possible drug etiology was called to his attention, he analyzed the chart in reference to the attacks of migrane and medication. He found that he could date each attack of illness, with and without the necrotic lesions, to the use of amidopyrine or other derivatives. When the tooth was extracted in June, 1933, he had taken 10 grains of amidopyrine and one and one-half grains of phenobarbital.

All drugs have been eliminated. This patient has now been followed for more than a year, and he has had no recurrence of symptoms.

Treatment—The results of the treatment of granulopenia will depend upon the type and extent of marrow damage, the recuperative power of the injured marrow, the seriousness of secondary infection, and the general condition of the patient. The first move in every case is to find and to remove the cause of the marrow injury if possible. Often the cause is obvious. In most cases of cryptic or so-called idiopathic granulopenia, the cause has not been recognized until a short time before the patient appears for examination. This type was formerly considered a uniformly fatal condition, as the use of the terms malignant and pernicious indicate. If the marrow is damaged beyond repair and secondary infections have supervened, the patient is necessarily beyond recovery. It is this type which has become associated in the mind of the clinician with the word agranulocytosis. In the cases reported earlier, we now know that the use of the very drug or drugs responsible for the initial marrow injury often was continued during the course of the disease, thus entirely precluding recovery. The marrow injury occurs in all degrees of severity, so there is no longer any reason to consider it a uniformly fatal disease.

Other than removal of the cause, all therapeutic measures are directed towards improving the general condition of the patient and stimulating the bone marrow to repair and normal activity. From the supportive standpoint, transfusion of blood is a most valuable procedure and should be used in all patients who are seriously ill. Transfusion should be given frequently during the active stages of the disease. Nutritious food and abundant fluids are necessary. Glucose and saline solution should be given intravenously and in large amounts if the patient does not have a sufficient food and fluid intake.

Numerous specific measures stimulating to the marrow have been used. X-ray has been tried but probably is of little value. Nucleotide therapy helps in some cases as is evidenced by the increase in leukocytes following its injection. Since its introduction, we have employed this in the form of pentnucleotide in all cases and have found it of help in some and valueless in other cases. Jackson and Parker[12] recommended

its intramuscular injection in doses of 10 cc. three times a day until the white cell count has been normal for several days. If the count is below 1,000, or the patient is extremely ill, they recommend using from 40 to 50 cc. daily which is administered intramuscularly or in small amounts intravenously. In giving pentnucleotide intravenously, 20 cc. is diluted in 1,000 cc. of isotonic saline solution and given at the rate of 50 to 100 drops per minute.

More recently, intramuscular injections of liver extract have been tried and found to be of value. I have seen several patients who responded to liver therapy after failure of response to pentnucleotide. The liver extract should be given in large doses such as 10 cc. of Lederle's parenteral liver extract each day, or 3 cc. every four hours, and frequent blood counts should be made to gauge the effect.

It is, of course, most important to treat adequately the secondary infections such as the nasopharyngeal lesions. Smears from such lesions usually show spirochetes and fusiform bacilli. For this reason, neoarsphenamine is usually recommended. This is an unwise procedure because of the great danger of causing further bone marrow damage.

The treatment may be summarized as follows:

1. Removal of the cause, if possible, with especial attention to amidopyrine.

2. General supportive measures, such as transfusions, forced fluids and adequate feeding.

3. Specific stimulating measures for the bone marrow:
   (a) pentnucleotide
   (b) liver extract

4. Treatment of the complicating secondary infections.

Discussion

Granulopenia or agranulocytosis should not be considered a definite etiological or clinical entity. The clinical and marrow picture is one which may be observed in identical form in numerous pathological conditions. The so-called idiopathic granulopenia does not differ clinically or pathologically from other granulopenias in which the cause is known. The condition is idiopathic only in the sense that the cause is unknown. Many such cases have already been explained as due to drugs, and so they are removed from the true idiopathic group.

The granulopenia, which has been emphasized, is in turn due to marrow injury and this, after all, is the most important feature of the disease. The granulopenia is of importance only as it reflects marrow injury, although the loss of the normal protective power against in-

fection explains the secondary infections. The marrow changes are very variable and depend upon the duration of the disease, the intensity of the marrow damage, as well as upon the amount which has been taken of the agent responsible for the marrow damage. While granulopenia as observed in the peripheral blood is always due to marrow involvement, the state of the marrow is not predictable from the blood findings. We should always think of the condition as a primary myelotoxicosis and try to find the substance responsible for the marrow injury. The blood findings are secondary, so the granulocytosis and the angina and other secondary infections are the result of the peripheral granulopenia.

Too much emphasis has been laid on the specific involvement of myeloid tissue in so-called idiopathic granulopenia. While it is true that the involvement of this tissue is out of proportion to the involvement of erythroblastic tissue and megakaryocytes, this is never absolute, and certainly cases in which there is no involvement of red cells and platelets blend into those having a marked depression of these elements. The toxic agents responsible for the condition do, however, have characteristically a selective affinity for white cell-forming tissues. Since the pathologic picture is identical in the myelotoxic granulopenias with known etiology and in those with unknown etiology, it is only a question of finding the toxic agents responsible for the picture in the unknown or idiopathic group. The clinical and pathological picture will vary with the amount and the toxicity of the causative agent as well as with the susceptibility of the patient to the agent; thus, every degree of marrow involvement may occur. The so-called malignant types differ from the mild types only in degree of intoxication and susceptibility of the individual to damage.

The susceptibility of reaction of the affected individual to the etiologic agents is probably the one most important factor in determining the amount of marrow damage. The incidence of hypersensitiveness to drugs in our group is most striking. Large doses of drugs which will injure myeloid tissue may, however, cause a granulopenia in individuals who are not drug sensitive, especially if they are taken over a long period of time. The condition usually, however, represents an unusual effect on the myeloid tissue in a drug sensitive person. The most significant development in relation to the disease is the demonstration that such commonly used drugs as amidopyrine and phenobarbital will produce the disease. This fact well explains the high incidence of the condition in doctors and nurses who are more apt to use such drugs.

The essential nature of the disease is a myelotoxicosis. When one considers the activity and lability of the bone marrow, it is surprising

that the mechanism of white cell formation is not disturbed more frequently. Frequent hypersensitivity to drugs and the common use of drugs which can injure bone marrow explain the increasing incidence of granulopenia. Minor degrees of granulopenia must be exceedingly common, although they are seldom recognized.

There may be any degree of involvement of the marrow at the stage of origin, maturation, or delivery. Autopsy studies concern only the most serious cases. The bone marrow biopsies unfortunately show changes only in the one area examined, usually the sternum, and this is not necessarily the picture in the marrow of all bones. It should be emphasized also that the involvement of the granulocytes is qualitative as well as quantitative. The local lesions are due to a loss of protective power of the neutrophils, and this depends on qualitative as well as on quantitative variations. There may be marked secondary lesions when the total count is not any lower than is frequently observed in conditions such as Banti's disease in which secondary infections seldom occur. Here, while granulocytes may be present, they are unable to perform their normal function, due to some toxic action on them in the marrow. The pathologic findings recorded by Jaffé[8] well explain the condition of such granulocytes as do get into the circulation.

The importance of amidopyrine and similar drugs as the primary myelotoxic agent first emphasized by Madison and Squier[4] now seems well proved. Fitz-Hugh[13] incriminated amidopyrine in one-half of his cases, and Watkins[14] in 13 of 32 cases. It is the most common etiologic agent in our series. Sturgis and Isaacs[15] considered amidopyrine as the cause of the disease in 7 of 9 patients. Three of their patients after recovery were given small doses of the drugs and all again developed granulopenia due to idiosyncrasy to the drug. Smaller series of cases have been reported by others after the drug had been taken for some mild illness preceding the granulopenic syndrome and forgotten by the patient, so necessarily there is a group of cases in which the use of the drug is difficult of proof.

Pepper[16] was the first to call attention to the frequent occurrence of allergy in patients who had idiopathic granulopenia. This is a most important observation as it probably is usually the drug idiosyncrasy which determines the marrow damage by a drug or drugs which have a selective affinity for myeloid tissue, although very large amounts may cause trouble in individuals without drug idiosyncrasy.

Time will probably prove that all true so-called idiopathic granulopenia is due to the toxic action on the marrow of some drug. The list of drugs which will cause such an effect is increasing. Dinitrophenol has been reported in a few instances. It is interesting, as emphasized by Kracke,[3] that all such drugs contain the benzene ring.

Summary

The bone marrow is normally in a very labile state and relatively easily influenced by toxic agents—bacterial, chemical, or physical.

The leukocyte picture as observed in the circulating blood results from the condition of the marrow.

Idiopathic granulopenia (agranulocytosis) is not a clinical entity but a symptom complex in which the fundamental condition is a myelotoxicosis.

The ulceration characteristics of the leukopenic states are secondary to loss of the defensive power of the leukocytes which in turn is due to both quantitative and qualitative changes in the granulocytes.

The granulopenia may be part of a generalized aplasia of the marrow, an interference with delivery of granulocytes, or a specific depressing effect on myeloid tissue.

A classification of granulopenia and illustrative cases of each type is given.

In the so-called idiopathic granulopenia, the common cause is amidopyrine and similar drugs. In a few cases, however, the cause is not evident so the condition is idiopathic but only in the sense that the cause is unknown.

In treatment, the first essential is recognition and removal of the cause. The patient must be tided over by transfusion and other general measures until bone marrow repair can take place.

In some cases, pentnucleotide and liver extract may aid in the repair of the marrow by stimulating the maturating process.

Every patient with granulopenia should be carefully analyzed from the standpoint of possible etiologic factors and the state of the bone marrow.

References

1. Schultz, Werner and Versé: Ueber eigenartige Halserkrankungen. (a) Monozytenangina. (b) Gangräneszierende Prozesse und Defekt des Granulozytensystems, Deutsche med. Wchnschr., 48:1495-1496, 1922.
2. Doan, C. A.: Neutropenic state; its significance and therapeutic rationale, J.A.M.A., 99:194-202, 1932.
3. Kracke, R. R.: Experimental production of agranulocytosis, Am. J. Clin. Path., 2:11-30, 1932.
4. Madison, F. W. and Squier, T. L.: Etiology of primary granulocytopenia (agranulocytic angina), J.A.M.A., 102:755-759, 1934.
5. Sabin, F. R. and Doan, C. A.: Bone marrow as an organ, Proc. Soc. Exper. Biol. and Med., 25:121-125, 1927.
6. Fitz-Hugh, T., Jr. and Comroe, B. I.: Agranulocytic angina (pernicious leukopenia): study based on 18 cases with 9 necropsies, Am. J. M. Sc., 185:552-561, 1933.
7. Fitz-Hugh, T., Jr. and Krumbhaar, E. B.: Myeloid cell hyperplasia of bone marrow in agranulocytic angina, Am. J. M. Sc., 183:104-110, 1932.

8. Jaffé, R. H.: Bone marrow in agranulocytosis (pernicious leukopenia), Arch. Path., 16:611-629, 1933.

9. Fried, B. M. and Dameshek, W.: Experimental agranulocytosis; infection of rabbits with Salmonella suipestifer by way of blood stream, Arch. Int. Med., 49:94-112, 1932.

10. Schilowa, A.: Zur Frage der pathologisch-anatomischen Veranderungen bei Benzolvergiftung, Folia haemat., 42:297-309, 1930.

11. Anderson, D. H.: Benzol poisoning with hyperplasia of bone marrow, Am. J. Path., 10:101-112, 1934.

12. Jackson, H., Jr. and Parker, F. J.: Agranulocytosis: Its etiology and treatment, New England J. Med., 212:137-148, 1935.

13. Fitz-Hugh, T., Jr.: Drug idiosyncrasy, with special reference to amidopyrine, as cause of agranulocytic angina, Ann. Int. Med., 8:148-155, 1934.

14. Watkins, C. H.: Possible rôle of barbiturates and amidopyrine in causation of leukopenic states, Proc. Staff Meet. Mayo Clin., 8:713-714, 1933.

15. Sturgis, C. C. and Isaacs, R.: Observations concerning the etiology of agranulocytosis, Tr. A. Am. Physicians, 49:328-335, 1934.

16. Pepper, O. H. P.: Leukopenia—a review: with special reference to agranulocytic angina, California and West. Med., 35:82 (August), 173 (September) 1931.